CANCER OF THE LUNG

(Endemiology)

A SYMPOSIUM

edited by

Doctor Johs. Clemmesen

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INHALTSVERZEICHNIS

SUMMARY

SUMARIO

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SOMMARIO

THE ENDEMIOLOGY OF CANCER OF THE LUNG

In the distant past public campaigns against disease were not begun until the fatal consequences of some plague became acutely obvious to everyone Therefore the preven tion of such consequences was deplorably in efficient

A hundred years ago pioneers such as SEMMELWEISS and FLORENCE NIGHTINGALE achieved great results by applying common sense in the prevention of disease but it took a long time, many lives and great discoveries to persuade medical and lay opinion that ef ficient hygiene demands the collaboration of every link in the modern community from midwife and teacher to press and parliament from architects of schools to designers of sewage systems and churchyards and that no private interest should be allowed to benefit at the expense of public health

While this experience applies to the group of infectious diseases how different, and alas how similar is the position of the neoplastic group of diseases for which group however, long periods of exposure and of latency are characteristic in more than one way

According to HUEPER cancer of the lung under the name of « mala metallorum » was reported by Paracelsus in 1531 as occurring among miners in Schneeberg while authorities in the nearby Joachimsthal mines which h

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bronchial carcinoma as a new disease repor ted during the last decades to an increasing extent particularly among men in the greater conurbations of western communities

The subjects of international symposia in the field of pathodemography of cancer have changed from the general discussion on statistical ways and means in Copenhagen in 1946 and the patho demographical survey of cancer in the world made in Oxford in 1950 to the more delimited subject of the ende miology of cancer of the lung which was the topic of the symposium at Louvain in 1952 With this development both practical results and controversies have come within the orbit of patho demographical research in cancer

The increase in frequency of cancer of the lung reported from many countries must be admitted to be real in most cases, although the recorded frequency of this disease, like that of most others will to some extent depend also on the quality of medical services and diagnostic methods

In dealing with the questions raised by this increase it is however of the greatest importance not to neglect a number of simple but indisputable facts which cannot be disregarded whatever the explanation of its causes these facts which are referred to below, should be kept in mind in the evaluation of the papers and results of the symposium at Louvain

The most important are first that the incidence of carcinoma of the lung has not yet

of bronchial carcinoma may take decades from the first exposure to carcinogenic influences until the death of the patient

It seems to be beyond discussion that cancer of the lung is sometimes caused by occupational exposure to asbestos and chromates and occurs with higher frequency among gasworkers and miners in certain mines

Inspired by the experience of almost two centuries that combustion products are often carcinogenic other workers have postulated that various kinds of smoke may be concerned in the causation of bronchogenic cancer

The smoking of tobacco long suspected of causing cancer of the lip was first suggested

al MILLS and PORTER MC CONNELL et al SADOWSKY et al have produced statistical evidence of a relationship between the smoking of tobacco and bronchial carcinoma and this is probably as far as statistical evidence

with an open mind and that the results of research on the problem may be appreciated in an unbiased way and given the widest publicity possible

PERCIVALL POTT in 1775 disclosed the etiology of chimney sweep s cancer and prescribed methods for its prevention even if the academic proof of his theory was not produced until PASSEY in 1922 produced cancer in animals by soot — which may not even now be accepted as a proof by all research workers Our forefathers with practical sense realized the truth of a recent editorial statement in the British Medical Journal that all we « can do is to show that the probability of a causative connection between an agent and disease is so great that we are bound to take what preventive action we can accepting the theory as though the proof was absolute until further research leads to some modification »

To many a modern view the final proof of the etiology of chimney sweep s cancer was produced by its prevention

May we show the same practical sense as our forefathers and not look for direct proofs which are out of reach before we transmit experience into practical measures They would indeed be hard measures which would be intolerable could they give only a wellfounded hope of diminishing the very serious endemic of pulmonary cancer ahead

THE EDITORS

can be expected to take us It must be left to biologists to decide whether tobacco smoke can be said to cause carcinoma of the lung, or whether carcinoma of the lung can be expected to cause an increased consumption of tobacco, or whether both may be interrelated to a third factor. FLORY in a review in 1941 could point to several successful attemps to produce neoplastic processes of benign or malignant character in animals by means of combustion products of tobacco

Atmospheric pollution with smoke has also been suspected of causing carcinoma of the lung , and it is hardly surprising that the smoke of town air contains a wellknown carcinogen as 3 4 benzpyrene, as shown by GOULDEN and TIPLER and WALLER It seems difficult, however, to visualize how this could cause a rise in lung cancer limited to the male sex, unless in combination with other carcinogens

Problems of this kind are not limited to a few countries, and it is only natural to attempt to solve them by international collaboration

The following diagrams will summarize part of the information presented at the symposium at Louvain It appears that national differences are reduced when urban areas are considered by themselves, so that similarities between nations prevail

It is such similarity, and such fruitful differences which form the justification for bringing together men and evidence from different countries, in the hope that the seriousness of this new, but delayed action menace to civilized mankind may be realized

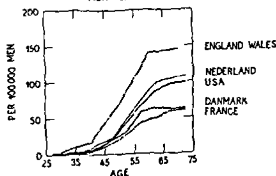


Fig 1

— — — England Wales, 1945-49 Lung and bronchus Stocks
Nederland, 1946-50 Lung, trachea, and mediastinum Neurdenburg
— — — U.S.A., White, 1949 Lung and bronchus Dorn
———— Danmark, 1946 50 Lung and bronchus Clemmesen et al
— — — — France, 1950 Lung and bronchus Denoix

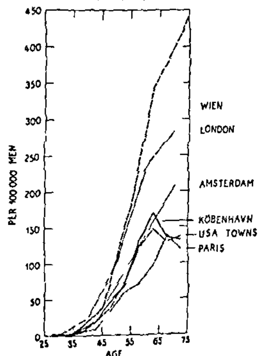


Fig 2

— — —— Vienna, 1951 Cancer of the respiratory system Kretz
— — — London, 1947 48 Cancer of lung and pleura Kennaway and Waller
Amsterdam 1950 Cancer of lung tra

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lung Denoix

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The purpose of the Symposium was to review our present knowledge on the Endemiology of Cancer of the Lung and to make precise proposals for the amplification of this knowledge

The field of the endemiology of cancer will be broadly defined as comprising knowledge concerning variations in the distribution and behaviour of cancer among various ethnological groups in different localities in relation to any relevant local factors

The first task of the Symposium was therefore, to sift available information in order to determine what evidence there is as to the extent and character of the increase in number of cases and deaths ascribed to cancer of the lung, observed during the last decades, mainly among males, in various countries and areas However, the Symposium considered it equally important to study in detail the nature of such factors which may contribute to an increase in the number of cases of can-

ping of cases of cancer of the lung

As a result of its studies the Symposium passed recommendations on the following subjects

1 Criteria for the acceptance and grouping of cases of cancer of the lung for endemiological studies
2 Publication of results of studies
3 Review of available information on the endemiology of cancer of the lung, and of some possibilities for further studies

RECOMMENDATIONS

Criteria for the acceptance and grouping of cases of cancer of the lung for endemiological studies

The Symposium on the Endemiology of

general considerations

The term « cancer » is synonymous with the term « malignant neoplasm », which includes carcinoma and sarcoma The term « carcinoma » is understood to be equivalent to the term « epithelioma » as used in some countries *to designate malignant epithelial tumours*

Cases of cancer of the larynx should not be classified under the same heading as cases of cancer of the lung The general classification « tumours of the respiratory tract » should be avoided

Cases of secondary cancer of the lung must always be clearly distinguished from cases of primary cancer of the lung

Histological examination constitutes the most valid proof of the existence of a cancer of the lung and should be made use of whenever possible

The Symposium taking these general considerations into account adopted the following recommendations

Recommendation 1.

The Symposium on the Endemiology of Cancer of the Lung

Recommends

1 1 That each case of carcinoma of the lung be classified anatomically in accordance with the « International Statistical Classification of Diseases, Injuries, and Causes of Death » established in 1948, as revised in 1952 The headings under which these cases may be listed are the following

162 Malignant neoplasm of trachea and of bronchus and lung specified as primary
— 0 Trachea
— 1 Bronchus and lung
— 2 *Pleura*

163 Malignant neoplasm of lung and bronchus, unspecified as to whether primary or secondary,

165 Malignant neoplasm of thoracic organs (secondary)

In order to determine the anatomical site of cancer of the lung most accurately the

SYMPOSIUM ON THE ENDEMIOLOGY OF CANCER OF THE LUNG

The Symposium on the Endemiology of Cancer of the Lung was convened by the Council of the International Organizations of Medical Sciences (C I O M S) (*), thus giving effect to a recommendation by the Committee on Geographical Pathology of Cancer under the International Cancer Research Commission of the International Union against Cancer

The Symposium held its sessions at Institut du Cancer, Louvain, Belgium, from July 21st

CLEMMESEN

The following members were present

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J C

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MARVIN KUSCHNER, M D, Consultant in Pathology, Institute of Industrial Medicine,

(*) Formerly O C.I C.M S.

an edition of the « Manual of Tumour Nomenclature and Coding » in order to meet the need of each country

1 5 That endeavour should be made to subdivide cases of primary cancer of the lung according to the degree of clinical

Publication of Results of Studies

The Symposium considered the methods available for statistical studies of geographical and other variations in the incidence of cancer and adopted the following recommendation

Recommendation 2

The Symposium on the Endemiology of Cancer of the Lung considering that it is desirable to obtain a high degree of comparability of results of study in the field of endemiology of cancer and being in full agreement on this point with the Symposium on

resolve to reaffirm the recommendation 2 adopted by the said Symposium in Oxford and thus

Recommends

2 1 That all authors and editors of future

each site being indicated by its code number in the International Statistical Classification of Diseases

2 1 1 Total number of new cases in the area being studied during the period examined

2 1 2 Distribution of the total population and of patients in the area with respect to race sex and age

2 1 3 Percentage of cases diagnosed in hospital

2 1 4 Percentage of cases diagnosed by histological examination

2 1 5 Percentage of cases verified by autopsy

2 1 6 Description of any subdivision undertaken (social occupational geographical etc)

2 1 7 Statement on the type and location of hospitals from which statistics have been gathered

(Considerations as given in Report of Symposium on Geographical Pathology and Demography of Cancer Oxford 1950 sep vol VII of ACTA Internat Un ag Cancer 1951 and Journ Nat Cancer Inst vol 11 p 627 1950)

This recommendation was adopted as the result of the following considerations

It was realized that the increasing efficiency in the therapy of cancer tends to make

if such studies are made for rural and urban population appropriate adjustments should be made for deaths of nonresidents

It was agreed that ideally studies of cancer incidence in a given area should contain

formation as to the total number of all sites within the material treated should be given whenever possible

In addition to full subdivision with respect to primary site a complete description should be given of the age preferably in quinquennial groups sex and racial composition of the general population from which the cancer cases have arisen

Cases with a diagnosis of « possible » or « probable » cancer may be shown by a total for each site but should not be included in

reliable statistical data for such cases alone usually will be unrepresentative of all cases of cancer developing in a population Special

following optional subheadings under item no 162 are suggested

A Tumour located in bronchi near the tracheal bifurcation

B Tumour located in bronchi but directly or indirectly accessible to endoscopy

C Tumour of broncho pulmonary location, not accessible to endoscopy

D Tumour of alveolar location

For example a carcinoma of the bronchus, located near the tracheo bifurcation would be grouped as 162 1 A

1 2 That in endemiological studies whenever *possible the validity of the diagnosis of* primary carcinoma of the lung should be classified according to the following system *of priority based on the methods* employed in establishing the diagnosis The following methods are available for establishing the diagnosis of primary carcinoma of the lung

1 Case history and physical examination
2 Radiological examination
3 Bronchoscopic examination without biopsy
4 Cytological examination of sputum and bronchial aspirates
5 Cytological examination of pleural fluid
6 Histological *examination of* metastases
7 Histological examination of the primary tumour (Thoracotomy)
8 Necropsy

The validity of diagnosis of primary carcinoma of the lung should be grouped following the order of priority given below

First

Positive result of histological examination of primary tumour of the lung

or positive result of histological examination of secondary tumour and evidence of primary tumour of the lung by radiological examination bronchoscopy, or thoracotomy,

or p[illegible]

tion bronchoscopy, or thoracotomy or autopsy

Second

Positive result of cytological examination only,

or positive result of radiological exami[illegible]

out biopsy

Third

Evidence based on case history and physical examination without further study death certificates as only evidence

1 3 That *so far as possible, the various ty*pes of primary carcinoma of the lung shall be grouped according to the following *histological classification*

a) Epidermoid carcinoma (epidermoid epithelioma)

b) Anaplastic carcinoma (anaplastic epithelioma large small and oat cell carcinoma)

c) *Adenocarcinoma (glandular epithelioma)*

d) Mixed forms combining some or all of the preceding types of cells

e) Other forms

This histological classification should be superseded by the « Manual of Tumour Nomenclature and Coding » whenever *they are incongruous in the hope that an international agreement will be reached* on the proposed classification

1 4 That in order to implement the resolution on the classification of neoplasms *according to histological type* passed by the World Health Organization (WHO techn Rep Ser 1952 no 53, p 47)

1 4 1 The American Cancer Society be invited to cooperate with the World Health Organization in the distribution of copies of the « Manual of Tumour Nomenclature and Coding » throughout the world for *trial as recommended* by the World Health Organization

1 4 2 Lists of pathological terms actually used be drawn up in the various [illegible]

Determination of carbon in lung post mortem offers a useful means of evaluating the extent of smoke particle retention

Occupational hazards giving rise to lung carcinoma have been demonstrated in a number of industries, in particular in the handling of asbestos and chromates, in gas workers, in a factory refining nickel and in certain mines bearing radioactive ores New processes may not be proved to be free of risk of cancer for many years, and other occupational hazards cannot be considered to contribute more than a small proportion of all cases of carcinoma of the lung The important causes must be sought in such aspects of the environment, as are common to the majority of the population in countries in which a high incidence of the disease has been established

Environmental factors other than those mentioned, but as yet unknown, may, however, enter the human body through ingestion, skin contact etc to exert a carcinogenic influence on the lung, although in so far as is known the entry of environmental carcinogens into the human lung is by inhalation Lung tumours induced in animals by materials introduced by other routes do not appear to have counterparts in human experience, but such possibilities must be borne in mind Experimental studies should be conducted with special reference to inhalation techniques and to sites of deposition of inhaled particles in the respiratory tract and the susceptibility of a variety of species of animals should be tested Certain simpler procedures may be useful for preliminary investigation of suspect substances These simpler procedures include 1) intratracheal injections, 2) skin painting 3) subcutaneous injection, 4) the tissue transplant technique Experiments may also be conducted to examine the effect of 5) material deposited in the nose and oropharynx It must, however be rembered that it is man with whom we are ultimately concerned and that animal experiments should be interpreted in the light of observations made on the occurrence of the disease in man This need not preclude the taking of immediate precautions against hazards to man suggested by animal tests

Variations in susceptibility of the individual exposed to the influence of environmental factors should not be ignored and would seem to deserve further investigation, for example it is not known to what extent sex differences in incidence of cancer of the lung can be explained by differences between the two sexes with regard to smoking habits

Co action of etiologic factors should also be taken into consideration with a view to investigating the possibility that inhaled sub-

ce a possible latent period for carcinoma of the lung

Studies of the gross and histological types of tumours may be significant in the evaluation of results from other kinds of study, which should be carried out with full attention to the type of lesion Thus, studies on histological changes in the respiratory tract, which may result from the influence of tobacco smoking, and similar studies on individuals exposed to industrial hazards and not developing carcinoma of the lung may give significant results

In view of these considerations the Symposium adopted the following recommendation

Recommendation 3

The Symposium on the Endemiology of Cancer of the Lung

Recommends

3 1 That the Committee on Geographical Pathology of Cancer under the International Cancer Research Commission should stimulate the organization and execution of further studies on the following subjects with a view to the etiology and pathogenesis of primary cancer of the lung

3 1 1 The extent of the increase in incidence of primary cancer of the lung observed particularly among males in various countries and areas, or where such increase is not found, the conditions of its absence

3 1 2 The association between the smoking of tobacco especially cigarettes, and cancer of the lung

3 1 3 The atmospheric pollution in urban and industrial areas

3 1 4 The occupational or industrial exposure to hazards associated with an increased incidence of cancer of the lung

analysis of histologically confirmed cases may be useful in evaluating the reliability of the conclusions drawn from the total data, although the value of this test will vary with the percentage of cases verified histologically *Whenever possible, the percentage of cases* histologically confirmed should be stated for each site separately

When studies are made of the occurrence of cancer in various social classes, or other groupings, the criteria of such subdivisions should be clearly stated

Studies of cancer incidence in urban and rural areas should give the basis for this *classification as well as information concerning* such factors as density of population, character of industries in the area, the type of cultivation etc

When conclusions are drawn from hospital cases alone full information should be given concerning the extent of the area served and the type of cases admitted to the hospital

Publications should contain tables giving *the fundamental figures mentioned above for* the entire population as well as for the cancer patients, so that other workers will be able to make comparisons or analyses apart from those in the original publication Likewise, all formulas used in the computation of results should be given in full, so that readers can study both methods and results obtained

It is desirable also that results should be illustrated by diagrams or graphs so that readers specialized in other branches of cancer research may form an opinion of the results obtained without a detailed study of tables and figures The omission of these details in order to reduce the expense of printing will decrease the value of the paper concerned

Etiological Studies on Cancer of the Lung in Past and Future

The Symposium reviewed information available on the Endemiology of Cancer of the Lung, and arrived at the following conclusions

Progressive increase in number of cases and deaths ascribed to cancer of the lung has been *observed for several decades* mainly among males, in a number of countries and areas However, it seems equally clear that there has been — and that there is — considerable controversy as to whether this increase is real in nature or only apparent, i e

sents a real increase in the number of people suffering from primary cancer of the lung Further research as to the extent of this increase, or where it is not found the conditions of its absence, should be undertaken

The Symposium considered several possibilities with regard to etiological factors

The smoking of tobacco — especially cigarettes —

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the only cause of cancer of the lung, there is now evidence of an association between cigarette *smoking and cancer of the lung,* and that this association is in general proportional to the total consumption Further research on this subject is imperative

An extensive chemical analysis of the products *of all forms of tobacco smoking with* a view to establishing whether or not any known carcinogens such as 3 4 benzpyrene are present seems equally called for Fluorescence spectroscopy offers a sensitive means for detecting small quantities of some polycyclic hydrocarbons under favourable conditions , the methods based on absorption spectroscopy are considered to be more reliable

Atmospheric pollution is *most likely to de*rive from effluvia and smoke from factories and domestic fires and by exhaust fumes from petrol and Diesel engines

For these factors it is primarily desirable to establish definitely whether or not any

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Variations in susceptibility of the individual exposed to the influence of environmental factors should not be ignored and would seem to deserve further investigation, for example it is not known to what extent sex differences in incidence of cancer of the lung can be explained by differences between the two sexes with regard to smoking habits

Co-action of etiologic factors should also be taken into consideration with a view to investigating the possibility that inhaled substances may have a co-carcinogenic influence or that conditions within the lung may have such an effect, which ultimately may influence a possible latent period for carcinoma of the lung

Studies of the gross and histological types of tumours may be significant in the evaluation of results from other kinds of study, which should be carried out with full attention to the type of lesion Thus, studies on histological changes in the respiratory tract, which may result from the influence of tobacco smoking, and similar studies on individuals exposed to industrial hazards and not developing carcinoma of the lung may give significant results

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3 1 2 The association between the smoking of tobacco, especially cigarettes, and cancer of the lung

3 1 3 The atmospheric pollution in urban and industrial areas

3 1 4 The occupational or industrial exposure to hazards associated with an increased incidence of cancer of the lung.

3 1 5 Environmental factors yet unknown including any that may act through ingestion, skin contact etc

3 1 6 Variations in the susceptibility of individuals exposed to environmental factors causing cancer of the lung

3 1 7 Coaction of factors causing cancer of the lung

3 1 8 Histology of lung lesions caused by any of the categories of factors mentioned

3 2 That such studies be carried out as international cooperative and correlated studies in populations of higher and lower incidence of cancer of the lung with simultaneous investigation of as many of the possible causative factors as possible

OPENING ADDRESS

BY

J H MAISIN
(Professor at the University of Louvain Belgium — President of C I O M S)

I want only to say a few words to tell you how much we appreciate your coming here It is a great privilege for our university to have been selected as the seat of this important symposium on lung cancer Our rector who is outside the country for a few days regrets very much not being able to welcome you in this ancient university He will personally preside the dinner which is going to be offered to you the last evening of the session

Personally I am deeply honoured for having been chosen as your host for these few days

All what this Institute can offer you is going to be done All the personnel and all the rooms of the Institute are at your disposal My personnel will do everything possible to help you in your work I am only sorry to have been unable to do more

This symposium as you know has been organized by the Geographical Pathology Committee of the ICRC of the International Union against Cancer under the auspices of the CIOMS which means Council of the International Organizations of Medical Sciences This council has been created under the joint auspices of WHO and UNESCO to coordinate congresses and a certain number of the activities in medical science One important activity of this council along those lines has been the organization of symposiums These are meetings of a limited number of scientists all interested in a definite problem but belonging to different disciplines in order to confront their views on the chosen subject and by doing so to contribute to development of medical science It is through the help of CIOMS that this research group on geographical pathology has been created It is through its help that several other important

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you these few words about the activity of *the council of which I have the honour to* preside and in this capacity also I am particularly happy to welcome you here

It is in this spirit that I ask your chairman and all of you to feel at home in this place and that I wish you a very successful worl

THE PURPOSE OF THE SYMPOSIUM

BY

Harold L STEWART
(Chairman)

First of all I would like to thank Professor MAISIN on behalf of the whole symposium for making these splendid arrangements with the university and the citizens of the community who are faculty members The arrangements seem to be perfect and the proceedings of the conference should take place under the best possible circumstances

I should like to state briefly my understandings of this symposium I would place its subjects under two main headings

1) Improvements of statistics on cancer of the lung This item will include the question *which criteria should be fulfilled in the ad*mittance of a case of lung cancer for statistical purposes as well as other measures to make statistics from different geographical areas more reliable and uniform

2) Research on carcinogens which would explain the variations in the frequency of cancer of the lung Does the atmospheric dust in cities with a high frequency of lung cancer contain some carcinogen which would explain this frequency or must we look else where for the cause — for instance to tobacco or some other factor which must not neces sarily enter the body by inhalation but per haps by other routes

I make these points as suggestions which may be modified as we go on but I do pro pose that we make each point the subject of study by a committee

METHODS OF WORK

BY

Johannes CLEMMESEN
(Secretary)

We are at this symposium facing the most violent phenomenon in the history of cancer namely the rapid increase during the last decades of male deaths ascribed to cancer of the lung

It is our intention to study the endemio logy of cancer of the lung i e to study « va riations in the distribution and behaviour of cancer among various ethnological groups in different localities in relation to any relevant local factors with the ultimate aim of assis ting in the prevention of bronchogenic car cinoma » To this end we will review the information available and try to make precise proposals for steps which may be taken to increase our knowledge further

In a field of study where countries repre sent experimental animals the organizational aspects of the problems dealt with are as important as the plan of an experiment I shall therefore have to make a few remarks on organizational issues

Geographical pathology in the stricter sen se of the term is as you know the collection of information on local problems of pathology from various parts of the world but as far as cancer is concerned demographical me t [illegible]
([illegible]
l [illegible]
the population at risk if we are to carry out reliable comparisons between people in dif ferent areas.

However like other fundamental issues this dualism is often neglected One century ago authors like RIGONI STERN SIBLEY and WALSHE paid due attention to demographi cal facts in studying the endemiology of cancer but they failed because of the inade quacy of the medical apparatus at their dis posal Now good medical facilities are avai lable in most parts of the world but we are inclined to forget the statistical basis of our results

Already in 1927 Dr BRANDT of the Lat vian University in Riga wrote « It would be welcomed from the geopathological point of view if a competent authority — perhaps the League of Nations — would sift and tho roughly work up the material available on cancer of the lung in Europe for only in this way can we hope to clarify the genesis of cancer of the lung From this would then follow the necessary measures for the pre vention and fight against the disease »

These words were written by a biologist and it may not be surprising that they did not call for universal attention It is more astonishing that a statistical authority like Dr GREENWOOD who did so much valuable work for the League of Nations should be unnoticed when the following year he wrote « It is probable that by the gradual impro vement in accuracy and completeness of the medical statistics of all nations we can best prepare the way for a really illuminating survey of the cancer problem » As it will be seen the importance of the problem was realized in pathology and was realized in statistics but no coherent effort was made to dovetail these two fields of study

It is true however that in the meantime we have not entirely wasted time Now we know that the influenza epidemics of 1919 are not the main cause of the increase in deaths from cancer of the lung and we have

also seen that the extermination of tuberculosis in many countries has not decreased the incidence of lung cancer as was once expected

One might then wonder why a symposium such as this was not called for twenty or twentyfive years ago One reason was no doubt that some years ago it was more difficult than now to be reasonably sure that we are dealing with primary tumours of the lung and not with metastases Progress in the diagnosis of cancer of various sites has increased the reliability of our material on primary cancers of the lung by minimizing the number of cases in which we are dealing with metastases quite apart from the diagnostic progress with regard to carcinoma of the lung itself

The dualism between geographical pathology and
pect beca
dies are e
patho demographical studies require the collaboration of state agencies and wide organizations to give the financial backing and the practical basis for the studies While individual workers are inclined to want changes in order to examine conditions administrative people prefer consistency in arrangements and such dualism can be traced in many fields However it is our task to try to bridge it and efforts to this end have been made in both fields

In 1946 an Inter European symposium on what was then termed cancer statistics was called by the Danish Cancer Registry in Copenhagen in order to clear the ground for patho demographical studies on cancer A recommendation was given in by the British and Danish governments to the Interim Commission for WHO urging more uniformity and coordination in statistical work on cancer Accordingly WHO appointed a sub-committee on the registration of cancer cases This sub-committee has met twice and after having surveyed various aspects of statistics on cancer worked out a nomenclature for cancer registers Thus the instruments have been created in the patho-demographical field

A corresponding development has taken place in the field of geographical pathology The « Union Internationale contre le Cancer » has created an International Cancer Research Commission which in its turn put down a committee on geographical pathology This committee took the initiative to the Oxford Symposium on the geographical pathology and demography of cancer in 1950 which I believe you know of Besides reviewing information available this symposium made two major contributions A recommendation was passed in favour of creating small working groups on the endemiology of cancer and in a second recommendation lines were laid down for publications in the field of patho-demography of cancer

Thus the ground has been prepared for specialized research in these fields which will be necessary since there is reason to believe that there is no single cause in common to all cancers

This symposium was suggested on 3rd April but even before its opening the International Society for Geographical Pathology met in Liege last week and decided to hold their next meeting in 1951 in Washington D C with cancers of various sites as their subject Also in U S A a Cancer Prevention Committee has recently met and has dealt with problems of interest to our studies of cancer of the lung

It is therefore evident that the opportunity has now come to call the interest of clinical research workers to the problem of the endemiology of cancer Even if we rely on experimental workers for the cure of cancer it seems to be to clinicians and pathologists that we must look for the prevention of this group of diseases

It is natural from what has been said that

but may be inadequate in organizing research into problems when these have caused wide

search Commission Such extension might result in the creation of a body resembling an international scientific society on the patho-demography of cancer I would like to bring this problem to the attention of the symposium and suggest it is made the subject of recommendation

ETIOLOGICAL IMPLICATIONS OF THE GEOGRAPHICAL DISTRIBUTION OF LUNG CANCER

BY

Paul E STEINER
(The University of Chicago, Illinois, U S A)

GEOGRAPHIC, ETHNIC, AND ZOOLOGICAL DISTRIBUTION

Cancer of the lung is found in practically every country, in all numerically major ethnic groups and probably in every minor ethnic group as well Its occurrence is world-wide It has been reported on all continents, in most countries, and in many geographical subdivisions of those countries Thus it has been described in all of Europe, most of Asia, in Australia, the different parts of Africa, in South, Central and North America, the islands of the Caribbean, Indonesia, Iceland, the Philippines, and in other places It has been recognized in Caucasoid, Mongoloid, Negroid, and Malayan peoples, and in some aborigines (Cleland), *Fig 1* shows that no major area of the world is free of lung cancer References for these cancers are not given here because they can easily be found in the Quarterly Cumulative Index Medicus and other indices Within most countries even the smaller geographical units are known to exhibit examples of this neoplasm For example, every province in Canada, all of the forty-eight United States, and probably every county within these states is afflicted with this tumor Further comments on ethnic distribution are made in subsequent sections of this paper

Cancer of the lung is ubiquitous not only in mankind but probably also in animals, It has been recognized in many parts of the world in wild, domestic, and laboratory animals Strains of laboratory mice having a high spontaneous frequency of lung tumor have metastasized by modern methods of transportation to many parts of the world in recent years However, this tumor was widely found in mice prior to such artificial dissemination When lung tumors in mice were first described around the beginning of this century, they were found almost simultaneously in the United States by LIVINGOOD (1896), in France by HAALAND (1905), and elsewhere, indicating that on etiological factor was already then widespread The wide geographical distribution of cancer of the lung in wild and in domesticated animals is illustrated in *Fig 2* and tabulated in *Table 1* This list is, no doubt, incomplete Lung cancer probably occurs in animals in many parts of the world and in species in which it has not yet been reported It would be desirable if such cases would be placed on written record in the literature in order to determine the precise zoological distribution, geographical extent, and if not incidence at least species frequency relative to other kinds of tumor Inasmuch as the experimental work with

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re strains and special breeds

The data now available on lung tumors in animals are inadequate to reveal whether incidence is greatest in those species sharing man's environment most intimately namely,

by the older biological age commonly reached by these two species Geographical studies on cattle within a country having diverse climatic conditions, such as in the United States might be highly rewarding in yielding clues to possible pulmonary carcinogens

Since cancer of the lungs occurs everywhere in man and probably also in animals the deduction is made that an etiological factor is omnipresent Whatever the causative factor or factors be — genetical , chemical or physical carcinogens , viral , or other — they are disseminated everywhere and in threshold levels

Geographical Distribution of Lung Cancer in Man

EQUATORIAL SCALE

MERCATOR'S PROJECTION

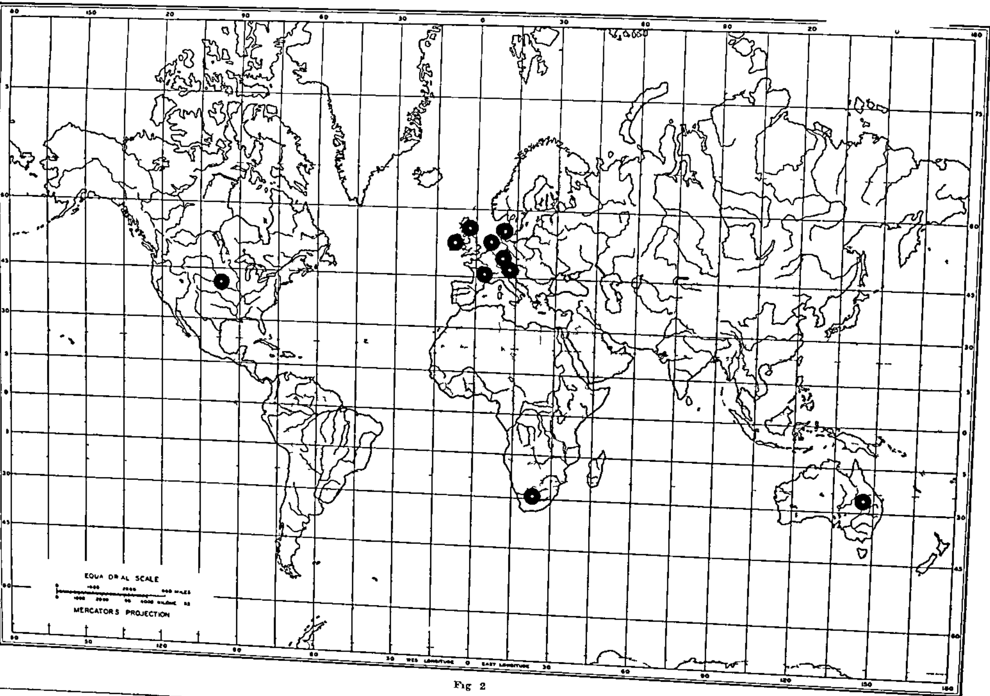


Fig 2

TABLE I

Geographical Distribution of Spontaneous Lung Tumors in Animals

Country	Author	Type of animal		
		Wild	Domestic	Laboratory
Australia	Apperly (1935)		Fowl	
	Willis (1948)		Dog	
Africa, South	Jackson (1936)		Dog, sheep	
Denmark	Sjolte (1944)	Jaguar	Dog horse, cattle	Guinea pig
France	Petit (1903)		Rabbit	
	Aynaud et al (1932)		*Sheep*	
Germany	Cohrs (1927, 1928)		Dog, sheep	
	Sticker (1902)		*Dog, horse,* cat, cattle	
Ireland and Scotland	Trotter (1911)		Cattle	
Netherlands	Bijl (1938)		Dog	
Switzerland	Jenny (1946)		Dog, horse	
United States	Feldman (193[illegible])		Dog, cattle	
	Feldman (1931)		Sheep	
	Fox (1923)	Kangaroo		
	Gilruth (1910)		Cow	
	Livingood (1896)			Mouse
	Mulligan (1949)		Dog	
	Ratcliffe (1933)	Civet, opossum, *bandicoot,etc*		
	Steiner and Bengston (1951)		Cattle, horse	
	Tyzzer (1907)			Mouse
	Wells et al (1941)			Mouse

GEOGRAPHICAL INCIDENCE, PREVALENCE, FREQUENCY, AND RELATIVE RANK

The distribution of lung cancer and there*fore of its causes is world wide, but the more* important problem remains whether its geographical frequency is equal or unequal and, [illegible]

lack of uniformity in reporting the demogra*phic data and in accuracy of the diagnosis of* cancer of the lung, a most serious defect in many of the publications is the use of geographical units which are too large In this way real regional differences may be hidden This aspect will be discussed in the subsection on recommendations for future studies

Incidence

Many papers have been written purporting to show geographical differences in incidence of cancer but fewer deal specifically with lung cancer Such a list is shown in *Table 2* (May) In this table the reported cancer death rate per 100,000 population in 1940 *varied from a high of 176 0 in Switzerland* to a low of 11 3 in Ceylon Do differences as large as that indeed exist ? They probably do not One wonders immediately how much of the difference is explained by the age factor, by differences in accuracy of diagnosis and reporting, and by other considerations apart from true cancer frequency Knowing that *cancer deaths per 100,000* population are said to increase from about 90 at age 40 years, to 150 at 60 years, 600 at 70 years, to 1,200 at age 80, the age factor alone may account for some of the reported regional differences

What has just been said for all cancer applies equally to lung cancer Probably the best data are those reported from England, *Denmark, and the Netherlands by* KENNAWAY, CLEMMESEN, KORTEWEG *and others I* shall not attempt to review the reported national differences in detail because that has

TABLE II

Cancer Death Rates by Country

Country	Reported Rate per 100 000 Population (From May)
Switzerland	176.0
England and Wales	172.3
Austria (1938 rate)	164
Scotland	162.7
Germany (1939 rate)	149.2
Denmark	147.4
Netherlands	138.2
Norway	136.2
Sweden	135.7
France	133.3
Ireland	127.6
Iceland	126.3
New Zealand	*120.2*
United States	120.0
Belgium	119.9
Canada	117.2
Australia	116.8
Union of S Africa	102.8
Finland	101.6
Hungary	101.3
Alaska (1945 rate)	99.5
Uruguay	98.8
Italy	86.2
Argentina (1936 rate)	85.4
Japan (proper)	70.9
Chile	69.7
Hawaii	67.[illegible]
Spain	65.3
Brazil (cities)	63.0
Greece (1938 rate)	5[illegible].3
Puerto Rico	51.1
Rumania	43.8
Panama (1943 rate)	33.6
Colombia	25.9
Venezuela	25.8
Egypt (to ns)	23.[illegible]
Mexico	23.2
Ecuador	19.2
Peru (1941 rate)	14.0
Ceylon	11.3

been done by others A few examples however are in order

Through the Danish Cancer Registry that country appears to have some of the best data on lung cancer The mortality in 1945 was 25 per 100 000 in males and 7 in females according to CLEMMESEN and BUSK (1947) These figures resemble those in *Table 3* from American cities The frequency was highest in Copenhagen less in provincial towns and least in rural areas The authors did not indicate whether this difference was real or whether it might be accounted for by inequality in accuracy of diagnosis and completeness of reporting

cer, including lung tumors STOCKS also found differences in the mortality levels between different geographical regions in England The mortality from lung cancer in proportion to cancer of all sites was lower in rural districts than in London or the County Boroughs A negative correlation was found between mortality from cancer of the lung and hours of sunshine Many others have compared lung cancer in rural and urban regions with varying results FRIESEN reported from the Canadian Province of Manitoba in 1947 that cancer deaths from respiratory tract cancer was 18 6 per 100,000 in the urban and only 10 2 in the rural population but he conceded that the diagnostic facilities were not equal DORN reported that the number of new cases of lung cancer reported each year in six different American cities bore no relation to geography or the relative amount of air pollution in those cities Further discussion of the evidence on this point is given by FALK and STEINER (1952)

According to DORN (1943) deaths from cancer of the lungs and pleura in 1939 40 in the United States was 6 2 per 100 000 population in males and 2 5 in females The prevalence rates for primary cancer of the lung in 1938 were 15 9 and 4 7 per 100 000 white population respectively for males and females The number of new cases of lung cancer per 100 000 white population per year were 10 8 and 2 9 for men and women respectively According to Dorn s figures about 8 000 new cases of lung cancer are recognized in the United States each year and 13 000 are under treatment

Geographical differences within the United States in the annual death rate were reported by MOUNTIN and DORN They divided the country into five regions and found that the rates per 100 000 population were 4 36 and 2 25 respectively in males and females in the Northeast states and 1 65 and 1 13 in Southern whites They recognized the possibility of regional differences in accuracy of reporting and drew no conclusions from their figures

In the United States geographical differences in lung cancer death rates have been

TABLE III

Prevalence, Incidence, and Mortality Rates of Lung Cancer in American Cities (per 100 000 Population) (*)

City	Prevalence			Mortality			Incidence			Percentage microscopical confirmation	
	1937	1947	Percentage increase	1937	1947	Percentage increase	1937	1947	Percentage increase	1937	1947
Atlanta	[illegible]	10.8	—	2.1	6.0	—	[illegible]	8.9	—	39	68
San Francisco**	11.6	[illegible]	218	[illegible]	13.8	[illegible]	9.8	20.8	212	60	72
New Orleans	[illegible]	24.0	133	5.0	13.6	172	7.6	20.8	174	40	67
Denver†	[illegible]	18.2	164	—	—	—	6.6	14.8	124	62	80
Pittsburg	—	18	—	—	10.8	—	8.1	15.7	94	41	58
Chicago	—	20	—	—	14.2	—	9.1	15.9	75	50	60

* Data obtained from «Cancer Illness», Cancer Morbidity series of 1950 1951 and 1952 Federal Security Agency, U S Public Health Service National Cancer Institute of the National Institutes of Health Bethesda 14 Maryland

** The earlier figures are for 1938

† The earlier figures are for 1931

reported by regions and by states by DORN and others A better source of information within the United States is the study on incidence prevalence, and mortality carried out by the U S Public Health Service in ten American cities in 1937-39 and repeated in 1947 The reports of the last survey have been published to date only for six cities The results for lung cancer are given in *Table 3* and compared with those of the previous survey The figures reveal geographical differences in mortality prevalence, and incidence of about 100 per cent It is uncertain how much these figures represent true differences and to what extent they are explained by inequality in diagnosis and voluntary reporting, and by the concentration of patients with this disease in medical centers in some of the cities studied Recognition of the value of surgical treatment in lung cancer is spreading rapidly but unequally through the medical profession and the patients have been referred, up until recently to relatively few medical centers, effecting a concentration of cases in these regions

Prevalence

The total amount of lung cancer present in a given population in a given period of time has been determined only a few times Since many lung cancers are still difficult to diagnose during life, any prevalence figure like incidence figures obtained would be an under-statement of the true situation The results of prevalence studies must, for the same reason, be a measure not only of the amount of lung cancer present in that population but also of the diagnostic acumen of the physicians, and for this reason alone geographical differences would be found Although the available data are too few to warrant wide geographical comparisons, a few studies should be mentioned

In *Table 3* a difference of over 100 per cent is seen in pulmonary cancer prevalence in six American cities These prevalence data are subject to the same criticism as those on incidence It is not certain that these differences are real The figures for prevalence in these cities are slightly less than twice those for mortality This is consistent with the known average survival of about nine months after the diagnosis is established, or about a year after the onset of symptoms (BUCHBERG et al, 1951)

Frequency

The frequency of pulmonic cancer can be

TABLE IV

Geographical Frequency of Lung Cancer in Necropsies

Country	Author	Place	Years	Total necropsies	Carcinoma of the Lung			
					Number	Per cent of all necropsies	Per cent of all tumors	Per cent of all carcinomas
Africa	Davies (1948)	Uganda	1931 1947	2,162	2	0 1	1 4	2 4
	Gelfand (1949)	So Rhodesia	1946 1948	2,000	5	0 2	6 8	7 8
	Strachan (1934)	So Africans	1924 1933	1,901	0	0 0	0 0	0 0
	Strachan (1934)	Europeans in So Africa	1924 1933	1,622	19	1.2	8 2	10 0
Australia	Cleland (1945)	Royal Adelaide Hosp	1920 1943	5,000	55	1 1	6 7	7 9
	Willis (1948)	U of Melbourne	1936 1944	—	—	—	7 5	—
Austria	Jaffé and Sternberg (1921)	Vienna	1915 1918	4,500	—	—	10 7	—
Canada	Boyd (1930)	Winnepeg Gen Hosp	—	900	14	1 5	—	—
	Klotz (1938)	U of Toronto	1926 1936	—	—	1 2	—	17 0
	McPhee and La Croix (1946)	Vancouver Gen Hosp	1934 1944	7,186	—	1 9	—	11 1
China	Hsieh et al (1940)	Peiping	—	—	—	—	2 6	—
	Kouwenaar (1950)	Sumatra	—	1,301	11	0 9	—	9 2
Czechoslovakia	Jeuther et al (1947)	Prague	1894 1943	35,819	362	1 0	6 4	7 0
Denmark	Husted and Bilmann (1937)	U of Copenhagen	1911 1933	5,709	29	0 5	3 1	—
	Eskelund (1942)		1934 1941	3,198	41	1 3	—	—
France	Waitz and Karczag (1938)	Strasbourg	1926 1936	9,378	55	0 6	7 0	—
Finland	Totterman (1948)	U of Helsinki	1904 1946	11,100	175	1 6	9 5	12 6
Germany	Emminger and Einfalt (1950)	Bavaria	1945 1947	—	—	—	—	19 8
	Knorr (1949)	Leipzig	1946 1947	1,529	60	3 9	—	18 9
	von Glinski (1939)	Stettin	1912 1938	20,519	184	0 9	6 8	—
Great Britain	Bonser (1938)	U of Leeds	1933 1937	3,118	74	2 3	11 3	—
	Dick (1940)	Glasgow	1929 1938	4,244	131	3 1	—	—
	El Gazayerli (1936)	Edinburg	1929 1933	3,156	61	1 9	10 6	—
Iceland	Dungal (1950)	U of Iceland	1932 1948	1,939	12	0 6	2 9	3 5
India	Gharpure (1948)	Bombay	1926 1946	4,321	0	0	0	0
Indonesia	Bonne (1937)	Java	—	—	4	—	—	3 1
	Kouwenaar (1950)	Sumatra	—	1,608	2	0 1	—	2.3
Italy	Fabris (1938)	Venice	1927 1937	10,000	150	1 5	—	—
Japan	Nagayo (1933)	Tokyo	1894 1932	12,077	86	0 7	—	5 5
	Nagayo (1933)	Fukuoka	1905 1915	2,017	8	0 4	—	2 4
	Nagayo (1933)	Kyoto	1901 1915	—	7	—	—	1 8
	Nagayo (1933)	Niigata	1912 1932	1,760	13	0 8	—	6 4
N W Indes	Hartz (1948)	Curacao	—	1,008	16	1 0	—	9 7
Panama	Tomlinson and Wilson (1945)	Panama	1929 1944	2,553	12	0.5	3 5	4 1
Philippines	De Leon (1933)	U of Philippines	1907 1927	13 004	6	0 1	2 0	3 0
Russia	Shih (1946)	Moscow	1938 1944	—	138	1 7	15 6	—
Switzerland	Wegelin (1942)	Bern	1935 1940	—	46	2 0	—	—
United States	Menne and Anderson (1941)	U of Oregon, Portland	1928 1940	7,971	83	1 0	—	—
	Bauer (1938)	Penn Hosp	1899 1938	6,000	32	0 5	6 0	—
	Brines and Kenning (1937)	Receiving Hosp Detroit	1937	3,000	25	0 8	—	—

TABLE IV

Geographical Frequency of Lung Cancer in Necropsies

Country	Author	Place	Years	Total necropsies	Carcinoma of the Lung: Number	Per cent of all necropsies	Per cent of all tumors	Per cent of all carcinomas
United States	Frissell and Knox (1937)	St Luke's, N Y C	1900 1935	3,695	39	1 1	—	6 6
	Gibson D M (1952)	Kansas City	1915 1950	12,812	120	0 9	6 5	—
	Halpert (1941)	*Charity Hosp* New Orleans	1931 1940	12,972	135	1 0	—	—
	Jaffé (1935)	Cook County Hosp Chic	1928 1934	6,800	100	1 5	—	11 5
	Joffe and Wells (1947)	St Luke s, Duluth	1940 1944	1,055	10	1 0	5 7	—
	Johnson and Rinehart (1943)	Ohio State U	1917 1942	8,333	66	0 9	—	8 3
	Koletsky (1938)	Cleveland City Hosp	1927 1937	7,685	100	1 3	9 3	—
	MacCallum (1930)	Johns Hopkins Hosp	1890 1930	11,254	30	0 3	—	3 9
	Matz (1938)	Veterans Adm, Washington	1927 1937	7 398	160	2 2	—	13 7
	McNamara (1943)	Dubuque, Ja	—	897	14	1 6	6 8	—
	Neely (1935)	U of Minn	1910 1931	16,916	80	0 5	—	—
	Olson (1935)	Boston City Hosp	1900 1934	7 893	69	0 9	—	9 1
	Perrone and Levinson (1942)	Mercy Hosp Pittsburg	1911 1939	2 694	38	1 4	—	10 6
	Rigdon and Kirchoff (1951)	Galveston	19[illegible] 1949	6,663	67	1 0	6 6	—
	Rosahn (1940)	Yale Univ	1917 1937	4,114	43	—	—	9 9
	Rosedale and McKay (1936)	Buffalo City Hosp	1925 1934	4,670	33	0 7	7 5	—
	Saxton et al (1950)	St Louis	1935 1950	12 443	242	2 0	10 4	—
	Steiner (1944)	U of Chicago	1901 1943	5,515	126	2 3	7 6	10 3
	Steiner et al. (1950)	Los Angeles County Hosp	1918 1946	36,864	508	1 4	8 4	—
	Wallace and Jackson (1943)	U of Texas	1942	5,000	28	0 6	6 0	—
	Weller (1929)	U of Mich	1892 1927	2,450	10	0 4	—	4 1
	Wheelock (1948)	Cleveland City Hosp	1948	3,384	57	1 7	—	—

expressed in relation to other things such as selected types of cancer, all cancer, all deaths in a population, all necropsies in a series, hospital admissions, etc Because the diagnosis of lung cancer is most accurate by postmortem examination, this discussion of frequency is limited to necropsy data The frequency of lung cancer relative to other forms of cancer in series of diagnoses from surgical pathological laboratories may be understated even when cytological examination of sputum, bronchoscopic biopsy, and exploratory thoracotomy are liberally practiced because the external and accessible forms of cancer predominate in such material

The frequency of lung cancer in twenty-two countries as compiled from 59 series of autopsies is given in *Table 4* Frequency is expressed in *relation* to all *necropsies, all* malignant neoplasms, and all carcinomas It should be pointed out that beside the geographical factor these necropsy populations differ in average age, sex ratio, and the time period in which they were performed — all of which effect the results

The table reveals a general constancy of

lung cancer in the different institutions provided the series are excluded which deal only with the early years of the present century and those confined to very recent years On the average lung cancer comprised about one, seven, and eight per cent respectively of all necropsies all malignant neoplasms, and all carcinomas Within the United States the results are essentially as elsewhere although racially this is a most heterogeneous group In this table some of the differences in the last two columns are caused by inability to determine whether the author used the word cancer as synonymous with carcinoma or with malignant neoplasm In future reports this distinction should be made clear

In a few necropsy series in *Table 4* lung cancer appears to be exceptionally infrequent Thus GHARPURE, on the basis of 4,321 necropsies in Bombay, reported no lung cancer, and in a series of 1,234 postmortem examinations which disclosed 68 malignant neoplasms in Lahore, Lucknow and Patna only one lung carcinoma was found by NATH and GREWAL, whose later papers however, unfortunately do not list this tumor separately These combined results appear to show an extraordinarily low frequency of this tumor in India If this becomes confirmed as fact it will be most interesting Only in Indonesia and in Uganda is lung cancer elsewhere so infrequent provided the older necropsy reports are disregarded

In no series in *Table 4* is lung cancer extraordinarily frequent, if recent short term reports are excluded It must be concluded that lung cancer is ubiquitous but it is impossible to state unequivocally on the basis of present frequency evidence based on necropsies that true differences do or do not exist

Relative Rank

The rank of lung cancer relative to other malignant neoplasms found at necropsy is commonly fourth or fifth although it shows wide fluctuation from this position Relative to carcinomas alone it occupies a rank one or two places higher In a few series of recent date in the United States it ranks second and even first, although its most common position in Caucasoids is fourth In Negroids its relative rank shows wide variation in different geographical locations ranging from about fourth in the United States to a similar position in the West Indies but a lower rank in Africa (STEINER, unpublished data and *Table 4*)

The frequency of lung tumors relative to all cancer or to all other causes of death is a valuable comparison but it is too crude to establish definite geographical differences Brief reviews by SIMONS and by STEINER (1944) explore this subject in some detail together with other statistical aspects

This brief and incomplete review of incidence, prevalence and frequency data leaves unanswered the important problem of whether real geographical differences exist after the necessary corrections are made They probably do but their size cannot be determined from the existing data except in a few instances The information obtained from these examples is so valuable in thinking about possible etiology that many additional statistical studies are desirable

RACIAL DIFFERENCES REVEALED BY NECROPSY STUDIES

Although frequency of lung tumors rela

TABLE V

Comparison of Cancer of the Lung in Caucasoids and Mexicans
(Los Angeles County Hospital, 1918 to 1947)

Race	Sex	Age 11 20	21 30	31-40	41-50	51-60	61 70	71 80	81 90	Totals	Per cent of all necropsies	Per cent of all tumors
Caucasoid	Male	3	4	12	56	116	9[illegible]	49	6	338	[illegible]0	10 8
	Female	1	[illegible]	3	10	16	[illegible]	13	4	[illegible]1	0[illegible]	3[illegible]
	Both	4	6	15	66	1[illegible]2	114	6	10	409	1 5	[illegible]9
Mexican	Male	0	1	3	10	1	9	4	0	44	1.3	14 6
	Female	0	2	0	6	8	[illegible]	3	0	[illegible]6	0 9	8 9
	Both	0	3	3	16	[illegible]5	16	7	0	[illegible]0	1 1	11 8

RATIOS OF NECROPSIES FOR LUNG CANCER TO ALL NECROPSIES BY RACE AND AGE
MALES

(LOS ANGELES COUNTY HOSPITAL 1918 1947)

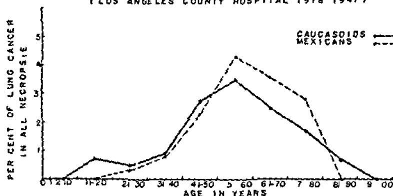


Fig 3

RATIOS OF NECROPSIES FOR LUNG CANCER TO ALL NECROPSIES BY RACE AND AGE
FEMALES

(LOS ANGELES COUNTY HOSPITAL 1918 1947)

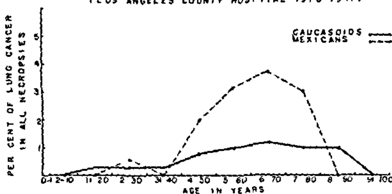


Fig 4

tive to all cancer or to other types of carci

Med Research from 1935 to 1939 on Indians from various regions Mohammedans Burmese, and other groups amply demonstrate that point

We have shown a high frequency of lung cancer in Mexican women dying in the Los Angeles area (STEINER P E in a forthco-

3

ming monograph on the « Racial Aspects of Cancer ») In 35,293 necropsies performed at the Los Angeles County Hospital from 1918 to 1947 on members of six ethnic groups, of which the Caucasoid and Mexican were the two largest, Mexican men had only slightly more lung cancer than Caucasoid males but Mexican females had significantly more (two times) than Caucasoid females and nearly as much as Mexican males (*Table 5* and *Figures 3* and *4*) In Mexicans the same relative statistical situation was found in the larynx as in the lung The causes for these racial differences are not yet known and no data are available from Mexico for comparison Two other races (Negroids, Japanese) were not recognizably different from Caucasoids in regard to lung cancer in the Los Angeles necropsies, and in two racial groups (Chinese, Filipinos) the material was not sufficient for separate analysis The Negro residing in the United States and in the Caribbean area appears to have a higher frequency of lung cancer in necropsies than does the African Negro This raises the question whether the disease is being under-diagnosed in Africa or whether there has been a real increase since migration to America Based on mortality data, DUBLIN (1948) reported that the five year averages of annual death rates (1941-1945) for lung cancer in age 1 74 years for insurance policyholders were greater in white than colored males but not in females The annual death rates per 100,000 in whites were 7 5 in males and 2 2 in females and in colored the corresponding figures were 1 3 and 2 0

The information available from Japan indicates that lung cancer is comparatively important in their total cancer problem Reports from China suggest that the frequency in that country is less than in Western countries, but data provided by BONNE on necropsies in Chinese residing in Java and in Singapore show a relatively high frequency These differences also suggest that either diagnosis is inadequate in China or that the ... places ... avai- ... fre-quency of lung cancer without, however, definitely establishing such a conclusion Comments have already been made on the apparent low frequency in India

The apparent increase in lung cancer in the Negro since migration to America together with a similar increase in gastric cancer but a decrease in liver cancer seems to indicate that these varieties of cancer are determined, at least in part, by environmental factors

CONTRIBUTION OF GEOGRAPHY TO THE QUESTION OF INCREASE

The question whether lung cancer is increasing has now been debated for about three decades and the problem is not yet solved Unanimity of opinion may never be achieved because real regional differences possibly exist with an increase in some places but not in others Here again is an example where thinking may have been too rigid, the methods of study too crude, and the geographical units under comparison too large to reveal subtle differences In some instances the data provided by the author have been inadequate so that the results are not comparable We agree with the statement of HEADY and KENNAWAY that the best index of change in frequency of lung cancer is the ratio of au-

... mortality surveys, but in many fewer necropsy studies Great improvement has occurred in recent decades in the clinical diagnosis of lung cancer but accuracy in the autopsy recognition of the major types has undergone little change, having started from a much higher level These facts cast doubt on whether the increase is disproportionate to other cancers Even in necropsy studies reported increases may not be real but represent merely a shift in the type of material that the clinical departments send to the autopsy room

The methods available for the diagnosis of lung cancer during life between the years 1900 and 1952 and their approximate order of introduction into widespread use was as follows

METHODS AVAILABLE FOR THE DIAGNOSIS OF LUNG CANCER

During Life

1 History plus physical examination
2 Cytological examination of pleural fluid
3 Biopsy of occasional distant metastases

4 X-rays
5 Aspiration biopsy
6 Bronchoscopic biopsy
7 Lobectomy and pneumonectomy
8 Cytological examination of bronchial washings and sputum
9 Exploratory thoracotomy

Four general comments should be made about these clinical diagnostic methods First, the order in which they attained widespread use differs somewhat from place to place , the order given is essentially that for Chicago Second, the methods did not have their maximum reliability from the time of first introduction but have achieved this gradually and some of them are still improving Third, in general the order of reliability of the methods increases from the top to the end of the list Fourth, a combination of methods is more reliable than any one alone except for histological examination of the primary tumor , the effects of introducing these new diagnostic methods were cumulative and mutually reinforcing

In *Figure 5* is shown a rough correlation of the introduction of these diagnostic methods by type and time with the reported

this neoplasm prior to 1920, that few were available before 1930, and that both the number of diagnostic aids and their reliability have increased sharply since that date, as has the number of reported deaths from cancer of the lung No claim is made that all of the increase was due to the introduction of these diagnostic methods, but this possibility is difficult to disprove The absence of an equally great increase in women speaks against this explanation

In a previous review of this question, the present writer pointed out (STEINER, 1944) some of the specific problems and he provided new data On the basis of 5,515 necropsies in the forty years 1902 to 1941 at the University of Chicago, the conclusions were reached that lung cancer had increased slightly in

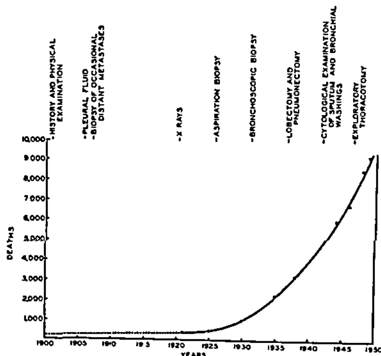


FIG 5 COMPARISON OF DEATHS FROM LUNG CANCER [ENGLAND AND WALES] IN MALES AND THE METHODS AVAILABLE FOR THE DIAGNOSIS OF LUNG CANCER DURING LIFE.

proportion to all cancers in males but not in females, and that the increase was less than that shown by intracranial tumors and carcinoma of the colon but greater than that for gastric and pancreatic carcinomas In a later report (STEINER et al 1950) based on 36,864 necropsies in the years 1918 to 1947 at the Los Angeles County Hospital, an increase was shown in lung cancer by quinquennia The increase was demonstrated in relation to all necropsies, all cancers, all hospital admissions and to four control types of neoplasms Because the same methods of analysis were used on the two sets of data, the conclusion was reached that real differences may exist in the two areas By essentially similar methods of analysis, SAXTON et al found in 12,443 autopsies in St Louis (1935 1950) that lung cancer had increased from 1 5 to 1 9 to 2 5 per cent of all autopsies in three five year periods, that two other types of cancer (pancreas, breast) had increased nearly as much as lung, and that all cancers combined had increased from 16 8 to 20 6 per cent of all necropsies during the period under study Gibson has recently reported an increase in Kansas City also

Recent necropsy studies from other countries demonstrate an increase in some cities and not in others Thus increases disproportionate to all cancer were reported by WILHELM in Adelaide, Australia, by JEUTHER et al in Prague, by KNORR in Leipzig and by EMMINGER and EINFALT in eight Bavarian pathological institutes Recent studies reporting no increase include those of BRYSON and SPENCER for London based on necropsies and that of CLEMMESEN and BUSK dealing with clinical diagnoses in Copenhagen where an apparent increase was attributed to improved diagnosis

In summary, it may be stated that most of the reports of studies based on the diagnosis of lung cancer made during life show an increase On the other hand, the studies based on autopsies vary some showing an apparent increase and others showing none Accuracy of diagnosis at postmortem examination has changed very little since 1900, but accuracy by clinical diagnosis has greatly improved because of the introduction of the methods shown in *Figure 5* Considering these facts, an increase in lung cancer disproportionate to that for all or selected types of cancer has not been demonstrated in most geographical regions, and perhaps even in none

Date of the Increase

In a previous paper on this subject (STEINER, 1944) it was pointed out that great geographical differences exist as to when the alleged increase in lung cancer began This fact, almost more than any other, casts doubt on the validity of a true increase The increase, if it is such seems to have arrived in most places with the awareness of the literature In some instances reported in the literature the increase was quite abrupt This is inconsistent with what is known about the induction time in carcinogenesis If this is true, the increase can be attributed to improvements in recognition of the disease The numerous examples of disparity in date of the increase cited in the previous paper in 1944, can now [illegible]
examples [illegible]
port that [illegible]
say it has stopped

It is possible that the key to this controversial subject lies in real regional differen[illegible]

cooperation in geographical studies It is highly desirable to know for each community if and when an increase began and whether it is continuing for our thinking about possible causes of this tumor

GEOGRAPHY OF MORPHOLOGICAL TYPES

No convincing evidence for differences in the gross or microscopical types of lung cancer associated with geography or with ethnic groups has come to my attention On the other hand the evidence is not conclusive that no such differences exist It appears that little though has been directed along this line Much more information is needed on this important point than is now available Such minor differences as stand recorded in the literature may be explained by variation in ideas on classification or terminology It is suggested that if studies of this type are to be of greater value in the future a uniform nomenclature must be adopted A classification such as that given in Fascicle 17 of the Atlas of Tumor Pathology on « Tumors of the Lower Respiratory Tract », by LIEBOW, 1952 or some other widely acceptable standard is needed Only if this is done can mor

phological comparisons become meaningful in the future

For the present it can be stated that the distribution of gross and microscopical types as reported from Russia by SHIH appears to be no different from that in Western Europe or America CHOISSIER stated that the morphology of cancers seen in the tropics (Haiti) was no different from that in temperate climates Similar statements can be culled from the literature but additional information is desirable

lung tumors induced by heavy doses of exogenous carcinogens may be multicentric in origin Certainly this is true of induced lung tumors in experimental animals where dozens of independent nodules may be produced It has also been alleged that lung cancers arising on the basis of old tuberculous scars are predominantly peripheral in location, and lepen Other have lidity of such assertions be established or disproved by additional data If they prove to be valid, such information can then be applied in other areas to a search for etiological factors

ETIOLOGICAL IMPLICATIONS

If lung cancer is due to genetical factors, these factors are present in every race and in many species of animals , if to mutation, the identical mutation occurs frequently and simultaneously in every country in man and animals , if to a virus, this virus has had world-wide dissemination and either it is adapted to many species of animals or a number of different lung cancer viruses exist , if to inhalation of atmospheric carcinogens, these agents are widely distributed and of diverse chemical composition

A strong case can be made from the geography of lung cancer for an etiological importance of environmental carcinogens This hypothesis appears to explain best the differences between cities or other regional units within countries It is impossible, however to exclude the possibility of other etiologic factors The changes in frequency within members of a race when they change environment by migration indicates that exogenous factors exist On the other hand, the possibility remains that differences exist in sensitivity of cells of different persons to neoplastic conversion, as exemplified by the lung cancers in infants No single explanation adequately accounts for the origin of all lung cancers

The geographical evidence already available on pulmonary carcinogens shows clearly that a number of etiological agents exist The recent comprehensive review of HUEPER (1951) on « Environmental Lung Cancer » gives about 250 references to the subject of established and questionable carcinogens and related topics Beginning with the now well-known Joachimsthal and Schneeberg lung tumors, an impressive list of specifically induced lung tumors has been recognized Since the Hueper review, the papers of GOULDEN, KENNAWAY and URQUHART on urban atmospheric arsenic, and of WALLER and of FALK and STEINER on 3 4-benzpyrene and other carcinogenic and related hydrocarbons in soot have drawn attention to additional possible pulmonary carcinogens WALLER demonstra-

ducts The statistical evidence for greater apparent carcinogenic activity of soot on skin than in lungs was explained by FALK and STEINER by the great adsorptive capacity of carbon blacks for polycyclic aromatic hydrocarbons requiring good lipid solvents for elution — a condition which may exist on the skin (sebum) but not in the lung In a previous attempt to extract carcinogens from human lungs, STEINER et al found slight evidence of activity in extracts of lungs but because activity was present also in the lungs of stillborn infants who had not inhaled atmospheric dusts, it was concluded that the agent was not exogenous In recent unpublished experiments we have demonstrated the presence of 3 4 benzpyrene in the anthracotic materials of a human lung which, however, had no cancer , in other lungs this compound was not found

In his report WALLER stated that he was unable to detect the presence of 3 4-benzpyrene in tobacco tars by the same methods that had been so fruitful with the other materials This has also been our experience

(in unpublished experiments) although similar tars were previously shown by FLORY in our laboratories and by others to exhibit mild carcinogenic activity on biological test in animals It is possible that this discrepancy in the results of chemical and biological testing is explained by the presence of a carcinogen in the tobacco tars which is not detected by the chemical methods used by WALLER and by us The statistical evidence for the etiologic role of tobacco will not be discussed here because this aspect can be better presented by others

The geographical distribution of lung cancer shows a close correlation with that of carcinoma of the larynx, lending support to the idea that they have similar causes The distribution of nasopharyngeal tumors on the other hand, is entirely different This tumor has a high frequency in South, West, and Central China and on Hainan island and in Chinese immigrants to Cuba, among Filipinos and Javanese, and in other geographical areas where lung cancer appears to be relatively infrequent

Use of Tobacco Other Than by Smoking

The possible etiologic role of tobacco smoking is covered by other speakers in this symposium and will not be here considered Any geographical study of cancer, however, reveals special examples of tumor induced in relation to the use of tobacco other than by smoking While they are not lung cancers, they are introduced here for whatever light they shed on the tobacco question

HELMAN described oral cancer consequent to the use of a hot metal pipe for smoking in Hottentot women of South West Africa Eighty per cent of these women who smoked showed leukoplakia which HELMAN attributed to the repeated contacts with hot metal The « reverse cigar smokers » or chutta cancer of the palate, also preceded by leukoplakia, was reported from India by KINI (1944) and by KHANOLKAR and SURYABAI (1945) The latter authors also described the khaini cancer of the inner surface of the lower lip at the site where pellets of tobacco and lime are maintained This is a reminder of the numerous claims that the danger of betel nut chewers cancer is greater in regions where tobacco is customarily included as a component of the cud

A possible etiologic relationship between pulmonary tuberculosis and cancer has long been considered but nearly abandoned However, many reports on the simultaneous occurrence of these two diseases continue to appear in the literature This is to be expected because of the high frequency of tuberculous stigmata, active or healed, in lungs In our routine necropsies, anatomical evidences of tuberculosis were found in nearly ninety per cent (STEINER et al, 1944) The residual lesions of this infection should, therefore, be found in many lungs with primary cancer Furthermore, the comparative geographical mortality from the two diseases appears to show an inverse relationship In our experience, some of the waxes and lipids of *Mycobacterium tuberculosis* stimulated great cell proliferation but induced no tumors (STEINER, P E, and HUGGINS, C Unpublished data)

Areas Free of Lung Cancer

Occasionally reports are made of large series of cancer diagnoses but containing no lung tumors Usually the diagnoses were clinical Thus SEHEULT reported 616 cases of cancer from Trinidad none of which were pulmonic COORAY studied microscopical sections in Ceylon on 2 295 malignant neoplasms which included 1,815 carcinomas in 31 sites and mentioned none in the lung although 18 were found in the larynx From Korea, LUDLOW, CHOY, and YUN all reported neither lung nor laryngeal cancers STRACHAN reported no lung cancers in 1,901 necropsies on South Africans, but it is known from later reports that these people do bear this neoplasm It is important to know whether these areas are truly free of pulmonic cancer or whether these reports represent merely failure of recognition

The ubiquitous distribution of lung cancer is informative about its possible causes, but complete absence in some area, if it occurred would be even more informative, especially

ther lung cancer does occur in every geographical region, even the smallest regional units

Etiologic Evidence from Lung Tumors in Children

Histologically verified cancers of the lung have been reported to occur in infants or children in Canada (Beardsley), Great Britain (CURRAN, SIMPSON, FIELD and QUILLIAM, JONES, DICK and MILLER), France

probability of causation by an inhaled exogenous carcinogen can almost certainly be excluded The short induction time suggests either an extraordinary high susceptibility or some unusually potent agent or both The widespread geographical origin of these cases indicates that the causative factors are widely disseminated The relative proportion of each histological type was about the same as is found in adults In view of the urethane-induced pulmonary tumors in newborn mice and rats whose mothers were injected with the chemical, the possibility of a trans placental influence must be entertained

GENERAL COMMENTS

An estimation was recently made of the national lung cancer problem in the United States (STEINER, 1952) It was found that the annual mortality was about 16 331, and the morbidity about 17,000 Further analysis showed that the present national average five year cures were about five per cent of all cases, that an additional 50 per cent might be cured if all available knowledge on detection, diagnosis, and treatment could be utilized, and that cure of the remainder, comprising 45 per cent of the whole, must await further research Similar estimates could be made for other countries From such studies estimates of the size of the research problem in lung cancer could be made for the whole world, and thus of the problem facing us at this conference

It is desirable to know accurately the frequency, prevalence, or incidence of cancer in each country for two reasons First, so that each country may know the size of its problem in therapy and control This is purely a national problem except in so far as information on improvements in prevention, detection, diagnosis, therapy, control, and education needs to cross nation boundaries Second, so that reliable information from all countries may be compared for the purpose of eliciting clues to etiology If true geographical differences exist, they must be due either

they must be explained on an environmental basis

Here is a situation where international cooperation is needed The scientific knowledge deductable from the pooled information will be greater than the sum of the component contributions

It is evident from this survey that great gaps exist in our knowledge of the geographical aspects of lung cancer, and that limited deductions can be drawn On the other hand it is equally evident that even the little that is known can suggest many problems and settle a few to demonstrate the profitable potentialities of this method of attack

A word of warning should be given on the misinterpretation of the role of histological verification in statistical work on lung cancer A high percentage of histological verification of the diagnosis in cancer of the lung is desirable, but it does not necessarily guarantee a total high diagnostic accuracy — even if it were to be 100 per cent Histological examination virtually eliminates the falsely diagnosed cases but this deletion is not greatly needed because it is known that over-diagnosis of this tumor is not great, at least in some localities A high percentage of histolo-

lung cancers that are being interred constitute the chief source of error The improved clinical diagnosis of cases in this group may account for much of the reported increase in lung cancer in recent years The increase may continue for some time because of further reduction in the error from this source

In 1948 total reported deaths in the United States numbered 1,444,337 of which 16,331 were attributed to lung cancer It is estimated that necropsy examinations were performed in about ten per cent of all deaths If this assumption is correct, about 1,299,901

persons were interred without autopsy If only one lung cancer went undiagnosed in each 100 of these deaths, about 45 per cent of lung cancers in the United States were unrecognized and unreported The actuality of this situation is not improbable And even if the necropsies performed were *twenty per cent* of all deaths the situation would be nearly as bad If these deductions are correct, the reported cases of lung cancer may nearly double from their present levels with further improvement in diagnosis without any in-

might indicate, it is known to all physicians *who perform postmortem examinations that* some cases of lung cancer are as yet undiagnosed during life In centers with excellent diagnostic facilities the proportion of such undiagnosed cases is small among the persons presenting themselves with primary chronic intrathoracic symptoms characteristic of lung cancer, but much greater in those that masquerade as extra thoracic diseases (osseous, nervous system, abdominal) or as acute intrathoracic disease (« pneumonia », abscess etc) The proportion of all primary lung cancers which are clinically of these extra pulmonic types is greater than is frequently appreciated

A number of statistical reports can be found in the literature on the accuracy of clinical diagnosis of carcinoma of the lung For example, POHLEN and EMERSON revie

ly diagnosed during life Over one third were missed SWARTHOUT and WEBSTER found that antemortem diagnoses were correct in only 72 per cent of cancers of the respiratory tract during the years 1933 to 1937 at the Los Angeles County Hospital These tumors were not subdivided into their constituent types but if this had been done the laryngeal cancers would probably have been higher and the lung carcinomas lower than that figure In the necropsy experience of WILLIS, carcinoma of the lung had been correctly diagnosed during life in only 61 per cent of cases As diagnosis improves carcinoma of the lung can *continue to increase as reported* in mortality clinical, and surgical pathological data for some time without an actual increase having occurred in the population

Reasonably convincing statistical evidence now exists for the causation of human lung cancers by radioactive materials, chromates, asbestos, arsenic, tar fumes, and some mixture *in which the active ingredient is not yet* known In some instances there is confirmatory experimental evidence It is not necessary to point out the geographical aspects of these discoveries, because they are well known, except to again emphasize the value of this method of gaining information Regarding chemical causes of lung cancer, it must be conceded that the combined known agents account for only a small percentage *of all cases*

In a volume on geographical pathology, I recently came upon a discussion of the incidence of cancer in Europe, the Faroe Islands, Iceland, Greenland, Turkey, Greece, Syria, Persia Arabia, India, China Egypt Tunis Algiers, Abyssinia, Mexico, Martinique, Barbadoes, Brazil, Peru, etc The author wrote on possible causes and on the question of an increase , the recent increase he attributed *to better diagnosis This book was written in* 1864 by AUGUST HIRSCH, Professor of Medicine in the University of Berlin The ques ... causes, effect ... yet been ... author would be impressed by the progress that has been made in lung cancer Probably more is known about the cause of this form of cancer than any other except cutaneous

RECOMMENDATIONS FOR FUTURE STUDIES

The following recommendations are made on the basis of the survey

1 In reporting, pooling of data from heterogeneous areas or geographical units ... re ... to- ... be ... the smallest possible ... nd statistical methods

2 Universal adoption of uniform nomenclature *is desirable, especially for the terms incidence rate, frequency* and *prevalence*

should be adopted such as (a) squamous cell carcinoma (b) adenocarcinoma (c) small undifferentiated cell carcinoma (d) large undifferentiated cell carcinoma (e) mixed cell carcinoma (f) alveolar carcinoma (g) carcinoma in bronchial adenoma (h) sarcoma

It is desirable to urge universal re adoption of the broad term carcinoma of the lung in preference to bronchogenic carcinoma Many malignant epithelial tumors of the lung arise from bronchi a few originate from alveoli and some arise from sites as yet undetermined The term carcinoma of the lung covers all these situations whereas the term bronchogenic carcinoma does not As more early lung cancers are discovered removed and studied the greater is the proportion of cases found to arise away from the hilum This indicates that probably many of the cases which in the past were principally peribronchial in the hilar region and were regarded as primary in that location were in reality the extensions from a primary more peripheral in location

4 In reporting statistics the method of

wever since series of cases based on histopathological or cytological diagnosis from material obtained by thoracotomy bronchoscopy or smears of sputum bronchial washings or pleural fluid fail to include the cases of lung cancer which present themselves as some extrapulmonic disease (intracranial osseous abdominal and other forms) thus failing to detect about twenty per cent of the lung cancers reliance on clinical diagnoses even if supported by surgical pathological diagnoses should be avoided if possible Instead necropsy data which detect all cases

All cancers occurring in a population in a given period of time are included in one or another of the categories shown in *Table 6* In *Table 7* the accuracy of each of the diagnostic methods used in statistical work is shown It is seen that necropsy data are most likely to find all internal cancers However only rarely is it possible to perform postmor

TABLE VI

Total Cancers in Any Population Within a Selected Period of Time

The sum of	
1 All fatal cancers diagnosed and reported	
All fatal cancers diagnosed but not reported	
3 All fatal cancers not diagnosed and reported	
4 All clinical silent cancers in persons who died of other causes during that period of time	
5 All cancers that were cured during that time	
Minus	
6 All cases misdiagnosed cancer and so reported	
	100 per cent

TABLE VII

Relative Reliability of Diagnosis of Cancer by Different Methods

Type of study	Fatal cancers diagnosed and reported	Fatal cancers diagnosed but not reported	Fatal cancers not diagnosed or reported	Silent non fatal cancers	Cured cancers	Erroneously diagnosed cancers
Mortality statistics	x					x
Clinical diagnoses	x	+			x	x
Prevalence surveys	x	±		+	x	±
Surgical pathological studies	+	+			±	
Necropsy studies *	x	x	x	x	x	

+ Indicates that some of the tumors in this category may be included

* If supplemented by reliable clinical records of past illnesses

tem examinations in all persons dying in populations This defect can be partly compensated for by stating the conditions of the sampling — its adequacy and its deficiencies

quency Sir Ernest Kennaway and I have shown exactly the opposite results in a study from London teaching hospital records since the war

DR STEINER I was a medical student in the late 1920es when cancer of the lung was first frequently diagnosed clinically and later proved correct by autopsy Cancer of the colon and external cancers had been diagnosed during life since the 1880es

DR DENOIX I would like to emphasize the danger of using death rates for comparing one country with another In the table shown the year was 1940 and the death rate given for France was 133 Owing to war conditions it was difficult to issue a true figure In 1942 to 1943 there was more stability in France and the figures are more reliable about 170 that is about the same as in England This would tend to show that a high death rate from cancer occurs where there are good doctors and a high standard generally

DR LEVIN I should like to comment on the statement that the problem of the increase in the frequency of cancer of the lung is unsolved This is of course always true to some extent but we have more information on the etiology of cancer of the lung than on most other cancers An increase in the frequency of a disease is first attributed usually to improved diagnosis If we say that the increase in lung cancer is entirely due to improvements of diagnostic methods we must postulate that the diagnosis of cancer of the lung has improved much more in males than in females There is no evidence to support this The presumption is that a good case can be made for a real increase in the frequency of the disease

DR DOLL I should like to ask two questions Has Dr Steiner any information on the morphology of the lung cancers in Mexican women ? And has he any information on the smoking habits of these women ?

DR STEINER I have no information on

factor

DR DOLL The second question is whether Dr Steiner postulates an association between cancer of the lung and cancer of the larynx In a Factor Analysis of cancer death rates I have found a weak factor for cancer of the lung in England and Wales which shows no association with cancer of the larynx There is other evidence in England to support this —such as the varying incidence of the two conditions in town and country

SIR ERNEST KENNAWAY In England deaths from cancer of the lung are going up by about 1200 a year whereas deaths from cancer of the larynx are static The difference is remarkable

DR STEINER This may be because cancer of the larynx is an external cancer and has long been more correctly diagnosed

SIR ERNEST KENNAWAY The question we are here to discuss is whether there has been a marked change in diagnosis

DR STEINER I think it would be premature to state that cancer of the lung is increasing everywhere Many regions have not been studied One would expect to find regional differences

DR LEVIN I would reiterate that the increase in the incidence of this condition seems to me to be real Would it be possible to recommend a system in some countries or parts of countries to secure autopsies on a representative sample of all deaths and not just the most interesting cases It would be most valuable if possible

DR STEWART In answering Dr Levin's question what has your experience been Dr Steiner in doing autopsies in the different hospitals where you have worked ?

DR STEINER I have had autopsy experience in four different classes of medical practice One is in a large university medical centre another at a large private general hospital a third on a county charitable institution — where I would suggest that at the present time nearly half of the cases are

large

DR MAISIN In order to study geographical patholo- ... tries with ... instance C... unless we ... we also need a good correct and uniform nomenclature as well as sound statistical methods

I would like to add a question Has it been proved that cancer of the lung occurs in wild animals in their natural surroundings ?

DR STEINER The wild animals developing cancer of the lung were in captivity

DR SMITH It is interesting that many species of non inbred animal develop cancer of the lung It is suspected that the disease in man may be due to certain environmental factors not common to animals and I would therefore like to ask Dr Steiner to comment on the types of cancer of the lung seen in animals Are they adenomata as in mice or more comparable with human cases ?

DR STEINER Domestic animals develop adenocarcinoma like the human disease unlike the mouse adenoma

DR HAMMOND I agree with Dr Maisin I would like to see some recommendations on the statistical terms used such as « Incidence » « Prevalence » etc There is even more confusion here than in histological terminology

DR DENOIX Some of these terms are being considered by W H O Committee on Health Statistics

DR STEWART We should ask one of our committees to consider nomenclature as well as criteria of diagnosis

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ZUSAMMENFASSUNG

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pen ergeben unter Berucksichtigung der Aetiologie
Die hauptsachlichen Mangel an Mitteilungen uber geo

graphische und Rassenprobleme werden hervorgehoben. Speziell wird darauf hingewiesen, dass solche Erkundigungen eingezogen und veröffentlicht werden sollten.

SUMMARY

The available information on the geographical distribution of lung cancer is reviewed. The differences, in so far as they can be determined, in incidence, relative frequency, and types are considered from the viewpoint of their etiologic implications. The chief deficiencies in desirable geographical and racial data are pointed out. Specific recommendations are made for the future collection and publication of such data.

RESUMEN

El autor da cuenta de las informaciones de que se disponen desde el punto de vista de la distribución geográfica del cancer de pulmón. Las diferencias en aparición, frecuencia relativa y tipos de cánceres en tanto que pueden ser determinadas, son consideradas desde un punto de vista etiológico.

Las principales deficiencias de información en el terreno geográfico y racial son hechas notar. El autor recomienda especialmente recoger y publicar estas informaciones.

RÉSUMÉ

L'auteur fait un compte rendu des informations dont on dispose du point de vue de la distribution géographique du cancer du poumon. Les différences en incidence, fréquence relative et types de cancers, pour autant qu'elles puissent être déterminées, sont envisagées sous un angle étiologique.

Les principales déficiences de renseignements dans le domaine géographique et racial sont signalées. L'auteur recommande spécialement de recueillir et de publier ces renseignements.

RIASSUNTO

L'A. fa un resoconto delle informazioni sulla distribuzione geografica del cancro del polmone. Le differenze che possano essere determinate in base alla incidenza, frequenza relativa e tipi di cancro, vengono studiate da un punto di vista etiologico. Vengono messe in correlazione le deficienze più salienti di informazioni adeguate sia da un punto di vista geografico che razziale. L'A. si raccomanda caldamente perchè nel futuro tali dati vengano debitamente catalogati e pubblicati.

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés.

Nous le regrettons et nous en excusons vivement.

La Rédaction

AN EVALUATION OF CLAIMS FOR OCCUPATIONAL FACTORS IN CANCER OF THE LUNGS

BY

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The first intimation that an agent from the external environment might cause cancer in the lungs came from the experience of miners in the Schneeberg region of Saxony The first diagnosis of lung cancer was made there in 1879 by HARTING and HESSE Among several hundred miners dying over the 37 year period prior to 1913 ARNSTEIN found that carcinoma of the lungs accounted for about 40 % of all deaths He identified the majority of the lung tumors as squamous cell carcinomata

These findings prompted a search for lung cancer among the neighboring Joachimsthal miners in Bohemia who handled rather similar ores In 1932 a survey was made of the Joachimsthal miners and 323 of them were examined fluoroscopically Not a single case of lung cancer was found Nevertheless among 89 Joachimsthal miners dying between 1928 and 1938 lung cancer was found at autopsy of 43

Although cancer of the lungs has been recognized as an occupational disease among the miners in these two areas the specific cause is not entirely clear These mines contain radioactive ores and it has been held that radon is the principle cause of the cancers An excellent review of the subject has been published by LORENZ (1) who emphasized the possible contributory role of other factors such as radioactive or arsenical dusts pneumoconiosis and genetic influence deriving from inbreeding Aside from the experience in the Schneeberg and Joachimsthal areas lung cancer has not been associated with mining operations elsewhere

The next association of respiratory tract cancer with occupation derived from the experience of a plant in Great Britain engaged in the manufacture of copper sulfate and the refining of nickel No radioactive materials were present in the ores handled Up to the present time 52 cases of cancer of the nose or nasal sinuses and 93 cases of lung cancer have been reported from this plant (2) Since lung cancer is a relatively common disease notably in Great Britain detailed data on the population at risk in this plant would be needed to ascertain what proportion of the lung cases might be deemed excessive Cancers of the nose and nasal sinuses are however relatively uncommon in the general population and the occurrence of 52 cases of them among employees of one plant signalized the existence of an occupational cancer hazard

This matter was reviewed in 1938 by A J AMOR (3) who stated that over a period of 25 years copper had been extracted in this plant by sulfuric acid which contained arsenic The arsenic precipitated as a metallic arsenide which escaped as dust in the process of calcining AMOR suggested that arsenic probably in combination with copper was responsible for the tumors Nickel was extracted by conversion to the volatile com

sed the cancers AMOR stated that there was a history of exposure to nickel carbonyl in only one of the cancer cases up to the time of his publication (3) He further argued that there had been no cases of nasal cancer in Canadian nickel refineries where sulfuric acid extraction was not used He stated that the incidence of cancer of the lung and other sites in workers on the Canadian operations was lower than in the general population Detailed data on the number of man years involved in the Canadian experience have not been published and the same is true of a Norwegian nickel refinery from which 3 cases of squamous cell carcinoma of the lungs have recently been reported (5)

In 1921 the plant in Great Britain shifted to a grade of sulfuric acid free of arsenic and in 1924 rebuilt the calciners in a manner

to decrease escape of dust (3, also personal communications) *No case of nasal cancer and only two cases of lung cancer have occurred in workers who were first employed there after 1924* The latent period of the cancers that were recorded is given as 18 to 25 years *and only two cases of lung cancer have occur* pational tumor hazard in this plant has been substantially reduced Whether this reduction reflects a prolongation in the latent period or represents an actual decrease in the eventual tumor rate should be ascertainable within the next decade

Arsenic, known to be capable of causing cancer of the human skin (6), has been investigated in several situations for carcinogenicity upon other tissues In studies of mortality data from a British factory handling inorganic compounds of arsenic, HILL, PERRY and associates (7), (8) found that 29 per cent of deaths were attributed to cancer whereas cancer accounted for death in only 13 per cent of instances among control populations living in the same area The proportional excess was confined to workers exposed to arsenicals and was not found among employees of the same factory whose tasks did not involve such exposure Cancer of the respiratory tract (7 cases) and skin (3 cases) contributed the majority of the excess The authors call attention to the small numbers

system In the age group under 55, there were approximately twice as many cancer deaths in the plant population than would be expected on the basis of mortality data for the state as a whole The authors concluded, however, that this difference was not statistically significant by reason of the small size of the plant population relative to the state population

Data that may bear on the question of car-

in various counties of a state in the U S A where copper ores of high arsenic content are mined and smelted In counties containing smelters the rates were 46 and 115 In a county where mining was done, the rate was 48 6 A rate of 5 2 was found in a county where the major occupation was agriculture, and a rate of 10 9 in the United States as a whole HUEPER calls attention to the large quantities of arsenical fumes formerly released into the air by smelters in this state and suggests that these may have influenced the rates found

Ores of high arsenical content are mined in Sweden It is possible that studies conducted in that country may reveal data as to whether arsenic presents a respiratory cancer hazard I have explored this question with Professor SVEN FORSSMAN Professor Forssman states that mining of copper ores rich in arsenic began in Sweden in 1928, and smelting a few years later To date, there has been no evidence of an occupational cancer hazard Since these Swedish operations have now continued for 21 years under good medical supervision an integrated study of exposure records of workers, arsenical content of dusts and mortality experience over the next decade may provide a definitive answer as to hazardous levels of arsenic or indeed as to whether arsenic is carcinogenic for the human respiratory tract The question has wide interest, for it will be recalled that arsenical dusts have been thought to play a role in the occupational respiratory tract cancers of the Schneeberg and Joachimsthal mines and in the nickel refinery discussed above Furthermore, finished tobacco products have been found to contain considerable amounts of arsenic, a large percentage of which is volatilized into the smoke (11) It is probable that arsenic present in tobacco products derives largely from the use of arsenical insecticides upon tobacco crops

During the past 20 to 30 years there have been reports of cancer of the lungs in chromate workers in Germany, which have been claimed to have occupational etiology A detailed study of mortality experience among employees of six major chromate producers in the United States was recently conducted by MACHLE and GREGORIUS (12) This study concluded that cancer of the lung was substantially more frequent among chromate workers than in a control population provided by the records of a life insurance company

rate among the chromate workers was unduly high The authors felt that monochromates presented the hazard but the exact nature of the carcinogenic material has been discussed further and with differing points of view by others (10) These studies were restricted to chromate producing plants There is no data as to whether such a hazard exists for workers exposed to inhalation of chromates in other processes such as spraying chromate primers (paints)

In view of the German and American experience a survey was recently made of employees in three chromate plants in England (13) Chest X rays were made on 721 men representing nearly all those employed in these plants. 165 had worked in the industry for more than 20 years Only one case of lung cancer was found Another man died of lung cancer in the year following the survey The author states that the examined men will be followed for mortality experience It is tempting to recall the situation referred to above in which a fluoroscopic survey of Joachimsthal miners failed to detect any cases of lung cancer although many deaths from this disease occurred among these miners over the succeeding few years

The 1947 report of the Chief Inspector of Factories in Great Britain (11) called attention to the occurrence of primary lung cancer in 31 instances among 235 cases of asbestosis The lung cancer rate (13 2 %) in these asbestotic lungs contrasted with a rate of 1 32 % found in a large group of silicotic lungs reported through similar channels to the Inspector s Office The mortality rate for lung cancer in the general population of England and Wales can be calculated as 1 36 % on the basis of death statistics published by the Registrar General For these considerations the question has arisen as to whether asbestosis predisposes to carcinoma of the lungs I have elsewhere presented a detailed discussion of evidence available on this subject (15) Lung cancer has occasionally been described in autopsies upon asbestotics in Germany the United States and Canada but the cases have been too few to provide convincing evidence of the existence of an occupational tumor hazard for asbestos workers in these countries It must be remembered that working conditions tend to vary in different countries and at different times within a single country For example ventilation regulations for control of dust in asbestos work rooms were adopted in Great Britain in 1931 The number and severity of cases of asbestosis has decreased markedly since that time In 1950 the Factory Inspector s Office had a record of only a single case of lung cancer among individuals whose employment in the asbestos industry in Great Britain had taken place wholly in the period since ventilation regulations were instituted Immediately prior to the present conference I visited the Senior Medical Inspector, Dr E R A MEREWETHER and learned that additional cases had subsequently occurred These as well as the earlier ones will require careful analysis with reference to the population at risk

In a series of 126 cases of asbestosis reported from Finland by WEGELIUS (16) there were no instances of carcinoma Work with asbestos in Finland has however been conducted for a period of only 20 years The British cases of asbestosis dying with carcinoma of the lung had a mean exposure of 16 5 years compared with 13 4 years exposure for asbestotics dying with no evidence of lung cancer according to the Factory Inspector s Report for 1947 The most advanced cases of asbestosis in the Finnish series had an average exposure of only 11 5 years and there were only 9 individuals in this group Furthermore it must be noted that the British figures are based on autopsy records whereas the Finnish survey was based on radiographic examination of living persons who were actively at work

I am unaware of observations for lung cancer in asbestos workers in countries other than the above where mining of asbestos or manufacturing of asbestos articles is carried out Russia and Rhodesia are countries where such studies might be possible

It is noteworthy that our consideration of environmental factors in lung cancer has thus far taken up only inorganic compounds This is unusual in that the great majority of occupational tumors of other tissues have been traced to organic compounds Several types of exposures involving organic compounds notably tar and tarry materials have been considered to present occupational respiratory tract cancer hazards as reviewed by HUEPER (4) who cites a Japanese paper listing 21 cases of lung cancer found over a period of 6 years in workers exposed to inhalation

of distillation products of coal tar in generator gas plants of steel mills A greater than expected frequency of lung cancer was attributed to gas works stokers and coke oven chargers in Great Britain by the KENNAWAYS (17) Their paper presents an extensive analysis by occupational groups of all death certificates filed in the General Register Office for cancer of the lung and larynx in males between 1921 and 1938 The population at risk in the various occupations, from which the « expected » number of deaths for each occupational group was calculated, was estimated from census returns Judged on this basis, there was a less than expected frequency of lung cancer among cotton spinners and piecers This finding, as the KENNAWAYS point out, is of unusual interest in that such persons are engaged in an industry that has for many years had a serious skin cancer problem from use of carcinogenic oils to lubricate the spindles Skin exposure in these textile mills has been attributed in part to spray of oil from the spindles, but I am unaware of any measurements of the amounts of oil mist The question has importance, for HUGUENIN has recently described a series of cases of lung cancer in metal workers in France and suggested a relationship to their exposure to mists of cutting oils (18)

Quite recently, a new and previously unsuspected respiratory cancer hazard has been discovered and is about to be described in the *A M A Archives of Industrial Hygiene and Occupational Medicine* by WEIL, SMYTH and NALE These authors have permitted me to present their experience to this conference (Addendum their paper has appeared in *A M A Arch Indust Hyg and Occup Med 1952 5* 535-547) Among 71 men employed 5 or more years in a unit for production of isopropyl alcohol there have occurred 4 cases of nasal sinus cancer, one case of lung cancer, one case of laryngeal cancer and one papilloma of a vocal cord It would seem clear that an occupational factor must have operated to yield such a series of respiratory tract tumors in this small group of men Animal experiments have disclosed no carcinogenic action on the part of the alcohol itself, but an increase over the expected number of pulmonary adenomas was observed in a few groups [illegible]

The present paper has been concerned with evaluation of data derived from human experience, but investigations conducted upon animals have contributed to our knowledge and much additional information can be expected from them I have elsewhere published a review of experimental studies of lung cancer (19) To date, most experimentally induced lung tumors have been the pulmonary adenomas of mice, which bear little resemblance to the majority of human lung cancers Direct introduction of potent carcinogens into the lungs have generally elicited sarcomas rather than carcinomas

I should like to comment briefly upon a procedure we developed which has proved useful for experimental production of carcinomas from lung tissue Lungs are removed from mouse embryos cut fine and implanted into the thigh muscles of adult animals of the same inbred line (the C strain, obtainable from Jackson Laboratory, Bar Harbor, Maine U S A) When such tissue is implanted together with methylcholanthrene, benzpyrene or dibenzanthracene, the bronchial epithelium undergoes metaplasia and carcinomas of transitional cell or frankly squamous cell type develop This method, the « tissue transplant technique » has been described in detail elsewhere (20), (21) Obviously, inhalation techniques are essential for adequate study of materials suspected to present inhalation hazards These however, require elaborate equipment The tissue transplant technique is mentioned merely as an inexpensive and simple procedure that may serve as a useful screening measure for test of substances [illegible]

[illegible] cupational factors in cancer, namely that such studies require the integrated efforts not only of physicians, but also of industrial hygienists statisticians and personnel familiar with the technology of the various industrial operations involved Further, the interest and cooperation of management and labor is needed for effective study and control of such hazards as may exist. In an endeavor to bring together individuals from such diverse fields, the Cancer Prevention Committee was established in 1948 for the purpose of studying environmental particularly industrial factors in cancer The Proceedings of this committee were published in 1952 as the March

issue of the *A M A Archives of Industrial Hygiene and Occupational Medicine*

It is conceivable that studies in this field may disclose occupational tumor hazards not presently recognized and thereby afford further means for effective prevention of cancer On the other hand, the widespread occurrence of cancer, and especially of lung cancer, makes evident that many cases of this disease would occur no matter what the occupation

pensation practice, the reporting of occasional cases with implication of occupational etiology must be replaced by sound statistical study of occupational group experience Studies of inbred lines of mice have shown that genetically different strains living under normal conditions develope tumors of certain tissues with differing and predictable frequencies Exposure of such animals to carcinogens increases the frequency and time of appearance of the tumors for which they possess inherent potentialities Evidence for increase in tumor frequency over and above that found in properly selected control populations is needed when claims for new occupational factors in human cancer are considered

DISCUSSION

DR MORGAN I should like to say something more about the nickel risk The process for manufacturing nickel carbonyl was first evolved in 1900 The first cancer cases occurred in 1923 Earlier records showed a number of cases of lung fibrosis but these have diminished since cancer has been occurring The nickel ore comes from Canada to Swansea It contains very many other metals It is first ground into a very fine powder and in the old process the dust was very profuse The new type of calciner is nearly dust free as is also the present crushing and grinding

been expected anyhow

The shortest period of work in dust among the cases seen is 1-1 1/2 years The lag period is 18 to 25 years The particle size of the dust is 1 to 10 µ The ratio of lung to nose cases is 100 50

The nickel made at Swansea goes to other factories in London, Birmingham, and Glasgow, where precious metals are extracted, alloys made and so on No unusual incidence has been seen in these factories The conditions seem therefore, to be associated with the refining process at Swansea All the cases have been in calciners and grinders The pathological type of lung cancers have been mixed

DR LEVIN Do your findings support the hypothesis that arsenic is the cause?

DR MORGAN They could do

DR DOLL I have had the opportunity of

far as one can tell — is twenty times the expected incidence

With regard to arsenic I would mention a study made by Professor Bradford Hill of a small factory outside London, which has been handling arsenic for many years A greatly increased proportion of deaths from cancer was found among people who had been employed there and was due to skin and lung cancer

With regard to chromates, I would strongly support Dr Smith's remarks regarding the perils of relying on mass X ray of present industrial populations Dr Bidstrup in her British survey found only one case in a chromate factory But she is now following up the employees and is finding some deaths and we begin to think that our experience may not be so different from Dr Machle's

Our study of gasworkers was based on 831 deaths among pensioners who had been employed in a gasworks There were 25 deaths from lung cancer against an expected 13 8

causes of death

DR LEVIN Am I right in thinking that arsenic is not an experimental carcinogen?

DR STEWART As far as I know it is not

DR FIRKET I have seen several specimens of asbestos cancer of the lung in Professor Gough s laboratory in Cardiff The lower lobe was always the one affected Is this special localisation always found ?

DR SMITH No but I can give you no figures on distribution

DR FIRKET The suggestion has been made that beryllium is cancerproducing Profes-

DR CLEMMESEN Has Dr Smith got more detailed statistical information on the material he presented ? For instance the minimum and maximum latent periods — the age when tumours occurred etc

DR SMITH There is additional material on the chromate work in U.S Public Health Service report in 1948 by Machle and Gregorius The asbestos cases have not yet been reported in detail except in a short posthumous paper b Gloyne in the Lancet 1951

DR CLEMMESEN Would Dr Morgan s material justify the precise definition of a latent period ?

DR MORGAN I have some difficulty in presenting details as the material comes from an industrial firm but I hope to as soon as possible

DR MAISIN Could Dr Denoix give some information on the French workers who used Bordeaux mixture in preparing their vineyards ?

DR DENOIX I have no information on this at present, but cannot give a negative answer I will look into the question in S and S E France where many people work in a fog of copper sulphate

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ZUSAMMENFASSUNG

Die Karzinome der Atemwege wurden mit mehr oder weniger plausibler Argumentation den verschiedensten beruflichen Einflussen zugeschrieben In Anbetracht der Verschiedenheiten der Industrien wie auch der Materialien und der Verarbeitungsmethoden in den verschiedenen Landern sollten die aufgeworfenen Probleme in gewissen bevorzugten Gegenden studiert werden und es ware wunschenswert die Erfahrun[illegible]

m

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od

oder anderen Arbeitern mit radioaktiven Stoffen an anderen Orten hingelenkt Die Frage, ob durch das berufsbedingte

tikeln Karzinor

konnten muss

Vorkommnisse in U S A und in Schweden scheinen bestimmte Aufschlusse in dieser Richtung geben zu konnen Man hat festgestellt, dass unter den Arbeitern von Nickelraffinerien in Grossbritannien Karzinome des Respirationstraktes als Berufskrankheit auftreten, nicht aber in Kanada In Grossbritannien wurde ebenfalls die Asbestosis mit Lungenkarzinom in Zusammenhang gebracht, sonst aber nirgendswo Lungenkarzinom trat als Berufskrankheit auf bei Chromarbeitern in Deutschland und in U S A nicht aber in Grossbritannien Es ist sehr wunschenswert weitere Untersuchungen uber diese Probleme anzustellen unter bes

ten in

quantit

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Lungenkarzinome verantwortlich gemacht In Anbetracht der bekannten karzinogenen Eigenschaften gewisser Teerderivate sollte alles getan werden um solche Tumoren aufzufinden und zu verhüten überall dort wo entsprechende Expositionen vorkommen Neuerdings wurde in U S A behauptet dass bei der Herstellung von Isopropylalkohol Karzinome der Luftwege entstehen konnen

SUMMARY

Cancers of the respiratory tract have, with varying degrees of plausibility, been attributed to a variety of occupational factors Since the types of industrial operations as well as the materials and methods employed vary in distribution among various countries the several problems involved present certain preferred areas for study and in some instances merit comparison of experience in different areas

Occupational lung cancer among miners has thus far been restricted to the German and Bohemian uranium mines Attention is required for the detection or prevention of similar cancer among miners or other workers with radioactive materials elsewhere

The question of whether inhalation of arsenical dusts presents an occupational hazard of respiratory tract cancer requires further study Certain situations in the United States and in Sweden are indicated as affording approaches to this problem

Cancers of the respiratory tract have been found to occur on an occupational basis among nickel refinery workers in Great Britain but no such hazard has been evident in Canada Asbestosis has been associated with lung cancer in Great Britain but no such association has been manifest elsewhere Lung cancer has appeared as an occupational hazard for chromate workers in Germany and the United States but not in Great Britain Further studies of these problems are desirable with special reference to differences in operations and to qualitative and quantitative differences in exposure in the various areas

Coal tar fumes have been associated with lung cancer in several countries. In view of the known carcinogenicity of certain coal tar fractions, close attention should be given to detection and prevention of such tumors in any localities where such exposures may occur.

Production of isopropyl alcohol has recently been claimed to involve a respiratory tract cancer hazard in the United States.

RESUMEN

Los canceres de las vias respiratorias han sido asociados, por razones mas o mesnos justificadas a diferentes tipos de agentes profesionales. Dado que los tipos de operaciones industriales y que las materias primas y los métodos empleados varian de un pais a otro será preferible estudiar los diferentes problemas en ciertas regiones y en determinadas circunstancias, será ultil comparar los resultados obtenidos en las diferentes regiones.

El cancer profesional del pulmon se encuentra unicamente en las minas de uranio de Bohemia y de Alemania. Hay que llamar la atencion sobre el descubrimiento y la prevencion de este tipo de cancer en los obreros que utilizan otras substancias radioactivas en otros lugares. Son indispensables nuevos estudios para determinar si el polvo de arsénico constituye un peligro profesional capaz de hacer aparecer cánceres de vias respiratorias.

Se han observado cánceres de vías respiratorias en los obreros de las refinerias de níquel en Inglaterra. Este fenomenos no ha sido observado nunca en el Canadá. En Inglaterra se ha asociado la asbestosis al cancer de pulmón pero esta sociacion na se ha comprobado en ninguna otra parte. El cáncer de pulmón se senala como un peligro profesional en los obreros de la industria del cromo en Alemania y en los Estados Unidos pero no en Inglaterra.

Son indispensables otros estudios para elucidar estos problemas. Seria preciso insistir sobre todo en el análisis de las diferencias cualitativas y cuantitativas en los procedimientos y las diferencias en el tiempo de exposición al agente toxico en las distintas regiones. Los vapores de alquitran se han considerado como responsables de la apairicón del cáncer pulmonar en diversos paises.

Teniendo en cuenta esta accion cancerigena de determinadas fracciones del alquitran se deberia dedicar una gran atención al descubrimiento y la prevencion de estos tumores en los lugares en que es posible tal exposicion. Recientemente se ha pretendido en los Estados Unidos que la produccion de alcohol isopropilico constituiria un peligro para las vias respiratorias en el terreno del cancer.

RESUME

Les cancers des voies respiratoires ont pour des raisons plus ou moins plausibles été associés à differents types d'agents professionnels. Etant donné que les types d'operations industrielles, que les matieres premieres et les méthodes employées varient d'un pays a l'autre il serait preferable d'etudier les differents problemes dans certaines regions et dans certaines circonstances, il serait utile de comparer les resultats obtenus dans differentes régions.

Le cancer professionnel du poumon se rencontre uniquement dans les mines d'uranium de Bohême et d'Allemagne. Il faut attirer l'attention sur le dépistage et la prevention d'un pareil cancer chez les ouvriers utilisant d'autres substances radio actives dans d'autres endroits. De nouvelles etudes sont indispensables pour determiner si les poussieres d'arsenic constituent un danger professionnel capable de faire apparaître des cancers des voies respiratoires. Aux Etats Unis et en Suede, certains cas l'imposent comme apportant des vues nouvelles sur ce problème.

On a observé des cancers des voies respiratoires chez les ouvriers des raffineries de nickel en Grande Bretagne. Jamais ce phenomene n'a été mis en évidence au Canada. On a associé en Angleterre l'asbestose au cancer du poumon, mais cette association ne se revele nulle part ailleurs. Le cancer du poumon est signalé comme un danger professionnel chez les ouvriers de l'industrie du chrome en Allemagne et aux Etats Unis mais pas en Angleterre.

D'autres etudes sont indispensables pour elucider ces problemes. Il faudrait s'attacher specialement à l'analyse des differences qualitatives et quantitatives dans les procédés et les differences dans le temps d'exposition a l'agent toxique dans les differentes regions. Les fumees du goudron ont eté rendues responsables de l'apparition du cancer du poumon dans divers pays.

Tenant compte de cette action cancerigene de certaines fractions du goudron on devrait porter grande attention pour la detection et la prevention de ces tumeurs dans les endroits ou une pareille exposition est possible. Recemment on a pretendu aux Etats Unis que la production de l'alcool isopropyle constituerait un danger du point de vue cancer pour les voies respiratoires.

RIASSUNTO

I cancri delle vie respiratorie per ragioni piu o meno plausibili sono stati attribuiti alle piu svariate cause professionali. Poiche le attività industriali come pure i materiali lavorati ed i metodi impiegati variano in distribuzione a seconda dei paesi i diversi problemi connessi mostrano logicamente aree preferenziali di studio ed in alcuni casi meritano uno studio comparativo delle diverse esperienze a seconda delle differenti regioni. Il cancro professionale del polmone è stato fino ad ora circoscritto alle miniere di uranio della Germania e della Boemia. E' percio necessario mettere in rilievo questa coincidenza onde prevenire ed allontanare l'insorgenza di un cancro del genere negli operai che lavorano materiali radioattivi in altre regioni. Ulteriori studi sono oggi indispensabili onde accertare se la polvere di arsenico costituisca un serio

pericolo professionale, tale da favorire l'insorgenza del cancro del polmone Negli U S A ed in Svezia si sono verificati casi tali da suggerire nuove teorie su questo problema Sono stati osservati cancri delle vie respiratorie fra gli operai delle raffinerie di nickel in *Gran Bretagna Tale evenienza non si e mai riscontrata* nel Canada In Inghelterra l'asbestosi è stata messa in rapporto con l'insorgenza del cancro del polmone ma tale associazione non e stata mai riscontrata altrove

Il cancro del polmone d'altra parte viene segnalato come un rischio professionale negli operai dell'industria del cromo sia negli Stati Uniti che in Germania, ma non in Inghilterra Ulteriori studi si impongono in proposito con particolare riguardo alla analisi delle differenze qualitative e quantitative sul tipo di industria e sul tempo di esposizione all agente tossico nei diversi paesi Le esalazioni del fumo del catrame sono ritenute responsabili dell'insorgenza del cancro del polmone in diversi paesi Tenuto conto della azione cancerigena di determinate frazioni del catrame, e indispensabile adottare misure di controllo accuratissime onde mettere in evidenza e prevenire questi tumori nelle zone in cui l'esposizione alla loro azione *e piu facile a verificarsi*

Affermazione recente negli U S A e quella che la produzione dell alcool isopropilico possa costituire un notevole pericolo dal punto di vista della insorgenza del cancro delle vie respiratorie

Il nous a ete impossible, par suite de circonstances independantes de notre volonte, de faire figurer la totalite des traductions des Resumes

Nous le regrettons et nous en excusons vivement

La Redaction

STUDIES ON CANCER OF THE LUNG

BY

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(Pathological Department, St Bartholomew's Hospital, London, England.)

As an introduction to the problem, we have given below a brief outline of trends in lung cancer mortality in England and Wales during recent years The data used come mainly from the Registrar General's Statistical Reviews, which now give the distribution of mortality by sex, age and area of residence in considerable detail A more comprehensive study by Dr PERCY STOCKS (1) is in the press, and will be available shortly

The number of deaths in England and Wales attributed to lung cancer has increased very rapidly in the past few decades, from 500 in 1920 to over 12,000 in 1950, and in considering what this increase means, we should take into account the change in size and age structure of the population and improved standards of diagnosis as well as changes in any factors which might influence the disease itself Further interest attaches to the way in which the deaths are distributed by sex, age, area of residence, occupation and so on, as this may provide clues as to which factors are of importance Whilst it is difficult to assess the part played by improving diagnosis, the effects of changes in population may be avoided by considering age-specific deaths rates, as in *Table I*

These show a continuous upward movement in practically all age-groups, the increase being more rapid and uniform in men *(Fig 1)* than in women

TABLE I.

Cancer of the Lung, Bronchus and Pleura (excluding Mediastinum) in England and Wales, 1911 1947

Death Rates per Million Living by Sex and Age — Calculated from deaths as given in the Registrar General's Statistical Reviews without any adjustment for changes in the basis of classification during the period (notably in 1940)

Period	25-	35-	40	45-	50-	55-	60-	65-	70-	75-	80-	85+
						MALES						
1911 20	5	12	16	27	43	58	73	84	69	52	32	21
1921 25	6	18	27	44	66	87	101	114	97	85	51	31
1926 30	9	22	53	75	114	143	180	171	165	130	98	20
1931-35	14	54	87	187	256	348	364	355	350	278	191	169
1936-40	23	67	151	274	433	586	646	634	534	462	326	174
1941-45	25	80	189	387	595	884	1016	965	743	630	384	247
1946-47	24	101	235	514	856	1189	1433	1447	1073	891	605	336
						FEMALES						
1911 20	2	6	10	17	25	32	37	40	46	34	24	15
1921 25	3	4	11	21	26	34	49	51	50	39	20	64
1926-30	3	9	16	22	32	56	61	71	78	74	50	43
1931 35	5	13	25	41	55	78	118	132	118	121	96	67
1936-40	7	16	32	49	78	107	153	179	192	183	151	90
1941-45	9	22	36	57	93	124	170	201	226	204	172	143
1946-47	10	24	42	69	96	151	205	268	281	283	259	157

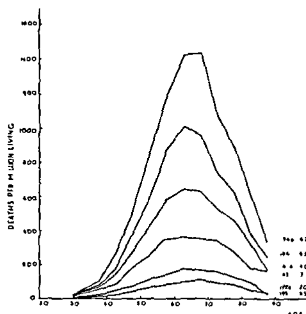


Fig. 1 (*)
Age Distribution of Mortality from Cancer of the Lung in Males in England and Wales

When the whole increase, and its distribution by sex and age are considered in the light of the work of WYNDER and GRAHAM and of DOLL and BRADFORD HILL on cigarette smoking, it seems very probable that it reflects the consequence of an increasing consumption of cigarettes, first amongst men, and later amongst women.

There are, however, other aspects to consider, and a regional analysis of lung cancer deaths in England and Wales shows considerable variations, which seem to be associated with the concentration of population. This is brought out clearly in *Table II*, in which mortality by broad age groups is compared for different classes of area.

The groups A to F represent aggregates at different levels of population density, arranged in descending order. Groups A and B comprise the six « conurbations » which have been defined in England, each of which consists of a number of administratively separate towns which merge into one another to form one large urban area. Groups C to F exclude any parts of the country which fall within these.

Fig. 2 illustrates the general tendency for mortality at all ages to decrease through the

TABLE II

Cancer of the Lung in England and Wales, 1950

Relative Mortality (England and Wales = 100) by Sex and Age in Groups of Differing Population Density — Based on preliminary figures supplied by the Registrar General

Group	Males			Females		
	45-64	65-74	75+	45-64	65-74	75+
A — Greater London	132	154	182	125	129	155
B — Other Conurbations	127	116	121	114	130	104
C — Towns over 100,000 population	118	119	109	100	90	103
D — Towns 50-100,000 population	93	84	71	88	84	80
E — Towns under 50,000 population	85	79	72	66	74	90
F — Rural areas	72	57	61	77	84	61
A to F — England & Wales	100	100	100	100	100	100
A to F — England & Wales Actual death rates per million	1247	2025	1202	155	341	334

(*) Fig. 3 shows the same data as fig. 1, together with approximate figures for some other years arranged on a cohort basis showing how high death rates have been experienced at younger ages in each successive cohort.

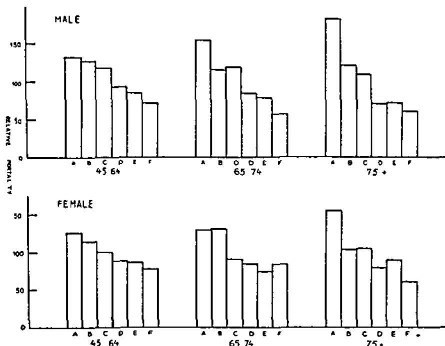


Fig 2

Mortality from Cancer of the Lung in Groups of Differing Population Density (See Table II)

several urban classes to rural areas The difference between the extremes is greater for men than for women and widens with ad

and (iii) some other factor associated with town life It seems likely that the wide differences which might at one time have existed under (i) are gradually being narrowed as time goes on whilst the same might also be true of (ii) Regarding (iii), it has often been suggested that town smoke may have some effect and some of the possibilities in this direction which have been explored are mentioned below

In England and Wales the death rate from cancer of the larynx has shown very little change compared with that of cancer of the lung during the past 20 years, and it is interesting to compare the two diseases with respect to town and country variations (2)

In *Table III* mortalities in urban and rural areas are expressed as a percentage of that in the County of London showing a progressive decrease towards rural districts

TABLE III

Cancer of the Lung and Larynx in England and Wales 1946 1949

Relative Mortality (London = 100) by Sex in Different Classes of Area

	Cancer of Lung		Cancer of Larynx	
	Male	Female	Male	Female
London	100	100	100	100
Other large towns	78	73	80	182
Other urban districts	63	64	68	170
Rural districts	43	54	59	238

in both sexes as regards cancer of the lung, and in men only as regards cancer of the larynx The latter shows the reverse rela

been detected in town air is 3 4 benzpyrene , (3) and (4) Quantitative estimations

of this compound in domestic soot, and in a large number of samples of smoke from London and 7 other towns have been made by methods based on fluorescence spectroscopy. An interesting feature of the results is the large variation between summer and winter at all places. Further, winter smoke contains a higher proportion of benzpyrene, which fact, taken with other evidence, shows that domestic smoke is probably the chief contributor of benzpyrene to the atmosphere. However, it has also been detected in the exhaust from petrol and Diesel engines, which then constitute another potential source of it. The relative importance of th...

is very different for domestic and exhaust smoke.

The general outcome of these investigations has been that the average concentration of benzpyrene tends to be higher in larger towns, but this may be modified by local conditions. An average concentration of smoke near the centre of a large town might be something like 20 mg/100 m^3, with a corresponding benzpyrene concentration of about 2.5 µg/100 m^3, and an arsenic concentration (see below) of about 6 µg/100 m^3.

Arsenic has also been estimated in smoke samples from 2 stations in London and 6 in other towns (5). The seasonal variations are rather less than in the case of benzpyrene, which difference suggests that arsenic is less predominantly a contribution from domestic smoke. The mean figures for the various towns ranged from 0.04 to 0.13 µg/m^3 As_2O_3. Ten cigarettes a day for one year will contain a maximum of 365 × 100 × 10 µg, or 365 mg of arsenic, of which 10 % (36.5 mg) might be volatilised (see below). This is about the amount which might be inhaled in a town in 70 years, for if we assume a daily intake of about 20 m^3 of air, the average figures quoted above indicate that about 100 g of suspended solids, chiefly carbon, but including something of the order of 12.5 mg of benzpyrene and 30 mg of arsenic, would be inhaled during this time. Clearly, only a small part of this will be retained in the lungs and bronchial glands. However, if this amount does not leave the body by any route, then that found post mortem is the actual amount retained in a lifetime. If the lungs and bronchial glands are dissolved in alcoholic KOH the solid matter, of which a very large fraction is carbon, can be centrifuged off, washed, and weighed.

In 12 adults examined so far, the carbon in the lungs has ranged from 5.0 g to 0.25 g, and in the glands from 0.3 to 0.007 g. If this « carbon » were of the type of the suspended matter in the air of towns described above, the maximum observed as yet (5 g) might have contained about 1 mg of benzpyrene, which is of the order of 500 times the minimum required to produce a sarcoma in a mouse. We are now obtaining material from persons of both sexes with and without cancer of the lung whose history in regard to (i) smoking, (ii) residence and (iii) occupation, is known.

The radioactivity of suspended matter in the air has been investigated also (6). This consists mainly of the short lived decay products of radon, and measurements have been made at 3 sites in London, at one in Manchester, and one in the country. The amounts are of the same order in urban and rural areas, and reach the highest level in closed rooms where one eighth of the official tolerance concentration of radon may be reached.

The amounts of arsenic and of radio active material which we inhale are very small, but we do not know whether any summation of their effects with those of benzpyrene and other carcinogens can occur.

The arsenic content of 31 brands of cigarettes from 11 countries has been found (7) to range from nil to 100 µg As_2O_3 (a cigarette weighs approximately one gram), and to show a transition from the arsenic rich American type in the West to the arsenic-poor Turkish type in the East, the lowest amounts (nil to 4.3 µg) being found in Turkish tobaccos (9 brands) and in cigarettes from France, Rhodesia, Bulgaria and Turkey. From 8 to 18 per cent of this arsenic is volatilised in smoking.

It is possible that one factor in the occupational incidence of lung cancer (8) may be connected with smoking. The incidence of cancer of the lung is low in (a) out-of-door workers (b) coal miners, and (c) cotton spinners and weavers (*Table IV*).

Coal miners cannot smoke when underground. However, those who work above ground, most of whom are not forbidden to smoke show as low an incidence of cancer of the lung. Cotton spinners and weavers

TABLE IV

Cancer of the Lung in England and Wales, 1921-1938

Occupations with Low Incidences.

Occupation	Ratio of registered to 100 calculated deaths
Coal miners, Hewers and Getters	69
Gardeners	60
Cotton (mule and other) Spinners	59
Coal miners (workers above ground)	56
Coal miners (others below ground)	45
Coal miners (conveying material to shaft)	44
Coal miners (making roads)	43
Cotton weavers	40
Farmers	40
Agricultural Labourers	29

cannot smoke in the mill, they may be exposed to fine droplets of carcinogenic oil, and are liable to cancer of the skin and scrotum An enquiry into the prevalence of cancer of the lung in occupations where smoking is, and is not, allowed, is in progress here The air of coal mines is pumped in from outside, and many coal mines are not in urban districts The low incidence upon coal-miners shows that the inverse relation of sunlight to cancer of the lung (9) is not due to direct action of light upon the skin No correlation has been found between cancer of the lung and pneumoconiosis in coal-miners (E L and N M KENNAWAY Unpublished results)

Some Proposals for the Planning of Research on the Causes of Cancer of the Lung

The association of cancer of the lung with tobacco, demonstrated especially by DOLL and BRADFORD HILL, and by WYNDER and GRAHAM, which is a very important advance in cancer research, at once suggests the problem to what extent the action of tobacco smoke in this respect is independent of any other factors, e g coal smoke For the present purpose, one must ignore agents, such as those to which nickel and chromate workers are exposed, which do not affect the general population

The following two questions seem to us to be the most important which the present Conference should consider

(i) Should laboratory workers concentrate wholly upon the examination of tobacco smoke for known (e g benzpyrene, arsenic) or as yet unknown carcinogens, or would it be more useful to investigate possible inter-relations between the effects of tobacco smoke and those of known carcinogens from other sources ?

(ii) What statistical enquiries, in what countries, would be most fruitful ?

In reply to (ii), we would suggest a comparative enquiry into

(a) consumption of tobacco, and

is high, and that there are no great linguistic, racial or religious differences such as may make the collection of data in such enquiries less easy.

A certain amount of material has been collected already, but we have failed to obtain

tem should be, and in what way to allow for the serious disturbance caused by the World War II

The data from Iceland must be numerically very scanty, but they are of quite peculiar value, owing to the absence of domestic and industrial coal smoke A good beginning has been made by Dungal Data from Sweden are also of peculiar value, because, at any rate until quite recent years, a large proportion of the tobacco consumed took the form of snuff, which was chewed If no data for cancer of the lung are available (there are none in the « *Epidemiological and Vital Statistics Report* » of W H O) the Symposium should be able to make an influencial request for the collection of such data

It should also be possible to obtain further information from detailed local comparisons of lung cancer mortality within single countries, such as Great Britain or the U S A, examining these in the light of observed local variations in smoking habits, atmospheric pollution and so on

The smoking of even a single cigarette, *produces, through the pituitary, a considerable* anti diuretic action (10) The potency of this effect suggests that one cannot wholly

ignore the possibility of broncho-motor or other effects upon the respiratory tract

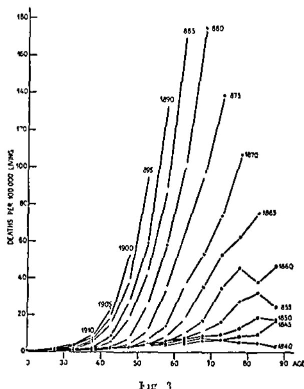


Fig 3
Mortality from lung cancer in male cohorts born around year indicated, England and Wales

DISCUSSION

DR CLEMMESEN The authors of this paper which represents an enourmous amount of work are to be congratulated One of the results we hoped to get from the Conference was to know whether such a project should be started in Scandinavia We can probably exclude the possibility for Iceland, because of the smallness of the population I would like to ask whether comparisons between England and Scotland and North-Ireland have been carried out

MR WALLER We admit the data from Iceland will be very scanty, but it seems to have some peculiar value Nothing much has been done regarding comparisons between England and Scotland and Northern-Ireland, the population of the latter being very small compared with England and Wales

DR STEWART Was there any reason for not including Finland ?

MR WALLER I do not know of any specific reason

DR CLEMMESEN Finland differs in many ways from the other Scandinavian countries However, they are making an effort to develop some sort of cancer registration, and the differences may prove to be of value to research

DR STEINER Have other hydrocarbons been identified in addition to benzpyrene ?

MR WALLER We have not found any of the more common carcinogens such as dibenzanthracene The methods of investigation have been strictly limited because the amount of these materials present is extremely small, the benzpyrene I have shown is only a very few micrograms Fluorescence spectroscopy which is very sensitive to benzpyrene and less so to most other carcinogens, is the only successfull method we have found in detecting this very small amount

DR STEINER Dr Falk in our laboratory (Cancer Res, 12 30, January, 1952) has been able to demonstrate the presence in carbon black of seven different aromatic hydrocarbons of which three are known to be carcinogenic While we need to start from a sound basis, we must not narrow our thinking too quickly and exclude other possible more potent carcinogens than 3 4 benzpyrene

Have you demonstrated benzpyrene in the soot obtained from any of these lungs ? We have done so in one case

MR WALLER No, but that is not to say it is not present An important factor is that ... ing upon very ... nt of adsorp ... size becomes very small It seems ... to determine whether the benzpyrene adsorbed in carbon is still biologically active I think Dr Steiner is interested in that question

Another factor involved is whether benzpyrene in smoke retained in the lung stays there indefinitely in every case It may be an inert chemical but during some fifty years it ...

ring that period

DR STEINER How did you arrive at the

figures of 12 1/2 milligrams of benzpyrene in the course of 70 years ?

MR WALLER That is derived from the amount of air breathed by a man during 24 hours, reckoned for a whole life time, and the average concentration of benzpyrene in some fairly large English towns There are very many factors involved and this gives only a rough order of magnitude

SIR ERNEST KENNAWAY A point of particular interest in regard to Sweden is that in 1908, 75 per cent of tobacco was taken in the form of snuff That figure has gradually come down to 32 to 34 per cent in 1949 It would be interesting to know what the cancer of the lung incidence is now We are very anxious to include Sweden in the enquiry

DR LEVIN I would like to ask whether the amounts of arsenic, involved in these calculations were discovered in post mortem examinations or not

SIR ERNEST KENNAWAY The figures were derived in the same manner as those for benzpyrene No estimations of arsenic at post mortem have been made by us

DR LEVIN It could be of interest to study the arsenic content of lungs at post mortem examination

SIR ERNEST KENNAWAY The figures are very rough It is the first attempt that has been made to work them out

DR STEINER In view of the difficulty in identifying benzpyrene this figure of 6 5 milligrams is probably a minimum figure

MR WALLER That figure is a maximum from one point of view, and a minimum from another Whether it approaches accuracy on those grounds, I do not know It represents the amount of benzpyrene a person has the opportunity of retaining In fact he only retains a very small proportion of it Further I would say that it represents only a small proportion of the benzpyrene that is present It is important to know in that respect whether the benzpyrene is fairly free or strongly adsorbed If there is a great deal more present we do not know whether it would be biologically active in that state

SIR ERNEST KENNAWAY We are only beginning the investigation of carbon Possibly harm is done not by the carbon found in the lung at death, but by what has passed over the mucous membranes of the bronchi

DR CLEMMESEN On the question of the chewing of snuff in Sweden, I believe this custom occurs most often [illegible]

[illegible] would also involve active investigation

I would like to ask about the accuracy of fluorescence spectroscopy in the hands of the not too experienced observer May we have details on fluorescence spectroscopy or other possible methods — if this is too delicate as a method — of receiving information

MR WALLER If there were sufficient material I would avoid fluorescence spectroscopy and would concentrate on absorption spectroscopy This particular investigation has been primarily directed towards getting some information about smoke in English towns, and because of th[illegible]

[illegible] be devised but these are extremely long term projects For exploratory work I think the method we used was the most satisfactory

DR CLEMMESEN I gather it would be technically possible to undertake international comparisons on this basis

MR WALLER Any international comparisons of atmospheric pollution would be long term projects and not very practicable I have not made any proposals for such work

DR CLEMMESEN These problems are sufficiently important to justify long term projects

DR HAMMOND I believe you said that the amount of arsenic in tobacco varied from zero in Turkish cigarettes to 100 micrograms in American cigarettes It is an interesting fact that death rates from lung cancer are higher in England than in the United States

Dr Doll said people in England tended to smoke their cigarettes lower down than in America I wondered if there was a difference in the amount of arsenic volatilised in the end as compared to the rest of the cigarettes?

MR WALLER Many American cigarettes are made in England from Virginia tobacco Those made in England may show more arsenic than those made in America The further a cigarette is smoked down the greater must be the *amount of arsenic volatilised* A cigarette end acts as a filter for a lot of tarry matter, but we have not found benzpyrene in them This does illustrate that the method of smoking a cigarette may be an important factor that we should look out for

DR MAISIN Would the use of a filter at the end of a cigarette prevent absorption of benzpyrene by the smoker ?

SIR ERNEST KENNAWAY It must help

MR WALLER The commercial type of filter is *intended* not to intercept too much material otherwise it takes away the satisfaction obtained from the cigarette I have intentionally made filters to retain as much of the tarry matter as possible, but if they retain 100 per cent there is no pleasure in smoking at all

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ZUSAMMENFASSUNG

Offizielle Statistiken fur England und Wales zeigen *eine rasche Zunahme der Todesfälle infolge Lungen*karzinom im Verlaufe der letzten Dekaden, wobei *Frauen und Manner betroffen werden, aber in ver*schiedenem Ausmasse In grossen Stadten wird eine wesentlich höhere Todesrate gefunden als in landlichen Gegenden fur alle Alterstufen Dabei nehmen kleinen Stadte eine Zwischenstellung ein

Bei diesen Verschiedenheiten spielen wahrscheinlich mehrere Faktoren eine Rolle und unter diesen werden athmosphärische Einflusse einer besonderen Betrachtung unterzogen Die Konzentration an karzinogenen 3 4 Benzpyrenen und Arsenverbindungen in der Luft vieler Stadte hat sich als ganz unterschied [illegible]

Die Schatzungen [illegible] fuhrten zu Mengenangaben von 0 bis 100 µg As_2O_3 pro Zigarette bei 31 verschiedenen Tabaksorten Die Untersuchung der Todesraten bei verschiedenen Berufen zeigten, dass diese *bei Kohlenbergwerksarbeitern* Baumwollarbeitern und Landarbeitern wesentlich un*ter dem Durchschnitt gelegen* sind *und es stellt sich* dabei die Frage, ob dies mit einer Verminderung des *Tabakkonsums in Zusammenhang zu bringen* ist.

Es werden Vorschlage gemacht fur weitere Labora*toriumsuntersuchungen an karzinogenen* Stoffen und es wird empfohlen Vergleiche anzustellen zwischen dem Tabakkonsum und der Haufigkeit des Lungenkarzinoms in vier verschiedenen skandinavischen Landern

SUMMARY

Official statistics for England and Wales show a rapid increase in deaths attributed to cancer of the lung during the past few decades, affecting both men and women but to different extents There is a much higher death rate at all ages in large towns than in rural areas with smaller towns taking intermediate positions

Several possible factors may *play a part in these* variations and amongst them air pollution has been

considered in some detail. The concentrations of the carcinogens 3:4-benzpyrene and arsenic in town air have been found to vary considerably between a number of towns of various sizes, and small amounts of radio-active material have been detected in the air in both town and country areas. Some knowledge of the total amount of smoke retained in a lifetime has been obtained from measurements of the amount of carbon in the lung post mortem.

Estimations of arsenic in cigarettes have shown a range of 0 to 100 µg As_2O_3 per cigarette amongst 31 different brands. A study of occupational death rates has shown that those of coal miners and cotton workers as well as agricultural workers are well below the average, and the question of the possible effect of restriction of smoking is raised.

Suggestions are made for further laboratory work on carcinogens, and a proposal is put forward for a comparative study of tobacco consumption and the incidence of lung cancer in four Scandinavian countries.

RESUMEN

Estadísticas oficiales de Inglaterra y del País de Gales demuestran un crecimiento rapido de la mortalidad por cancer pulmonar en las ultimas decadas y ello tanto en el varón como en la mujer aun cuando en proporciones diferentes. En todas las edades se observa una cifra de mortalidad mas elevada en las grandes ciudades que en las regiones rurales en tanto que las ciudades pequenas ocupan una posición intermedia.

Estas variaciones pueden ser influidas por diversos factores y los autores han tratado de estudiar detalladamente el aire y la polucion. La concentracion de los carcinogenos 3:4 benzopireno y arsenico en el aire de la ciudad, segun ha podido observarse, varia considerablemente en las distintas ciudades de distinta extensión y se han observado pequenas cantidades del substancias radioactivas en el aire de las zonas urbanas y rurales. Se ha llegado a conocer la cantidad total de humor retenido durante toda una vida por medio de mediciones de la cantidad de carbon en el pulmón cadaverico.

Las valoraciones del arsenico en los cigarrillos han demostrado la existencia de 0 a 100 miligramos de As_2O_3 por cigarrillo entre 31 tipos distintos. Un estudio de las cifras de mortalidad profesional ha demostrado que las de los mineros de carbón y de los obreros de algodón así como la de los agricultores estan muy por debajo de la cifra media y se plantea la cuestion sobre el posible efecto de la abstinencia en el uso del tabaco.

Se hacen sugerencias para ulteriores trabajos de laboratorio sobre carcinógenos y se propone un estudio comparativo del consumo de tabaco y de la frecuencia del cáncer pulmonar en cuatro paises escandinavos.

RESUME

Des statistiques officielles d'Angleterre et du Pays de Galles revèlent un accroissement rapide de la mort due au cancer du poumon au cours des quelques dernieres décades et cela chez l'homme comme chez la femme, mais dans des proportions différentes. A tous les âges on observe un taux de mortalite plus éleve dans les grandes villes que dans les regions rurales tandis que les petites villes occupent une position intermediaire.

Différents facteurs peuvent influencer ces variations, les auteurs se sont attaches à etudier en détail, la pollution de l'air.

Les auteurs ont montre que la teneur en substances cancerigenes 3:4 benzopyrène et arsenic, varie considerablement pour des villes d'importances differentes. Ils ont detecte de faibles quantites de substances radio actives dans l'air des villes et des regions rurales. Une certaine idée de la quantité totale de fumee retenue dans le poumon au cours d'une vie a pu etre obtenue grâce à une mesure de la quantite de carbone contenue dans les poumons a l'examen post mortem.

L'estimation de l'arsenic dans le tabac des cigarettes a montre des variations de 0 à 100 µg d'As_2O_3 par cigarette et ce, pour 31 mélanges différents de tabac. L'étude de la mortalite en rapport avec les occupations professionnelles a revele un taux nettement moins en dessous de la moyenne chez les mineurs, les ouvriers de l'industrie du coton et chez les agriculteurs, on peut se demander si ces observations sont a mettre en relation avec une reduction de consommation de tabac.

Les auteurs font des suggestions pour d'autres recherches de laboratoire portant sur l'etude des agents cancerigenes, et proposent aussi une etude comparee de la relation entre la consommation du tabac et l'incidence du cancer du poumon dans les 4 pays scandinaves.

RIASSUNTO

Le statistiche ufficiali d'Inghilterra e del Galles dimostrano un rapido aumento della mortalita per cancro del polmone nelle ultime [illegible]
e [illegible]
l [illegible]
e [illegible]
piccole occupano una posizione intermedia, a prescindere dall'età presa in esame.

Differenti fattori possono influire nel determinare tale variazione e gli AA. si sono rivolti in modo particolare a studiare il pulviscolo atmosferico, dimostrando che il tenore in sostanze cancerigne, quali il 3:4 benzopirene e arsenico variano considerevolmente nel le città di differente importanza. Sono state calcolate piccole quantita di materiale radioattivo nell'aria sia delle città che delle regioni rurali. Una valutazione relativa della quantità totale del fumo depositato nel

polmone durante la vita si può ottenere in base alla valutazione della quantità di carbone contenuto nei polmoni al riscontro autoptico

La valutazione dell'arsenico nel tabacco delle sigarette ha dimostrato delle variazioni da 0 a 100 per µg di AS_2O_3 nelle sigarette in 31 miscele di tabacco prese in esame

Lo studio della mortalità in rapporto con le occupazioni professionali ha dimostrato un tasso nettamente al disotto della media nei minatori, negli addetti all'industria del cotone e nei contadini sorge il quesito se queste osservazioni si debbono mettere in relazione con una riduzione nel consumo del tabacco

polmone nei quattro paesi scandinavi

Il nous a eté impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés

Nous le regrettons et nous en excusons vivement

La Rédaction

SMOKING AND CARCINOMA OF THE LUNG

BY

Richard DOLL

(Member of the Statistical Research Unit, Medical Research Council, London, England)

In an earlier paper DOLL and BRADFORD HILL (1950) reported on the association found between carcinoma of the lung and the amount of tobacco smoked in a series of 709 lung carcinoma patients and an equal number of control patients with other diseases Since then a further group of patients have been interviewed and a number of additional details have been elicited about patients' smoking habits The method used throughout the investigation is described in the earlier paper, a number of minor alterations were made in the latter part of the work and these are described in full in a paper to be published shortly in the *British Medical Journal* (2, 1271, 1952)

TABLE I

Numbers of Patients Interviewed in Each Disease Group

Disease Group	No of Cases Interviewed
Carcinoma of lung	1486
Carcinoma of other special sites	70
Carcinoma of uncertain primary site	36
Other diseases A (control group)	1465
Other diseases B	1282
Uncertain diagnosis (records untraced)	3
All groups	4342

The total numbers of patients interviewed in the various main disease groups are shown in *Table I* The greater part of the results reported here refer to 1,465 lung carcinoma

patients had not been paired with any comparable control patients at the time the investigation was completed and they are omitted from the analysis The 70 patients with « carcinoma of other special sites » suffered from carcinoma of sites within the thorax other than the lung or of other sites which have, at various times, been thought to be possibly related to smoking These patients, as also patients in whom the site of the primary growth was uncertain, have been excluded from the control series The group of patients referred to as « other diseases, B » consists of patients with various diseases other than lung-carcinoma who were interviewed but who were not included in the control group, it consists mainly of two large groups of patients with carcinoma of the stomach and of the rectum, who were interviewed for other special purposes *Table II* shows details of a number of characteristics, by which the comparability of the lung-carcinoma and of the control patients was tested It is seen that the sex and age distributions and the places of interview of the patients in the two series are exactly comparable (necessarily so because of the method of selection of the control group), that the social class distributions are approximately equal — the differences are not statistically significant — but that the places of residence of the patients in the two series are appreciably different The difference in distribution of the places of residence probably results from the fact that the patients were interviewed in hospitals in large centres and that the treatment of lung carcinoma patients is more centralised than the treatment of other diseases The absence of any marked deficiency of rural inhabitants in the lung-carcinoma series cannot, therefore, be taken to show that there is no difference of incidence between town and country The diffe-

smoke less than Londoners do

The principal result obtained from the comparison of the lung-carcinoma and the

TABLE II

Comparison between Lung carcinoma Patients and Patients with Other Diseases, Selected as Controls, with regard to Sex, Age, Social Class, Place of Interview and Place of Residence

Attribute for comparison	No of Lung carcinoma patients M	F	No of Control Patients M	F
Age				
25	17	3	17	3
35	116	15	116	15
45	493	38	493	38
55	545	34	545	34
65 74	186	18	186	18
All ages	1357	108	1357	108
Social Class (Registrar General's Categories)				
I	39	—	53	—
II	165	—	172	—
III	750	—	720	—
IV	172	—	198	—
V	231	—	214	—
All social classes	1357	—	1357	—

Attribute for comparison	No of Lung carcinoma patients M and F	No of Control patients M and F
Place of Interview		
Greater London	1035	1035
Bristol	73	73
Cambridge	36	36
Leeds	58	58
Newcastle	263	263
All places	1465	1465
Place of Residence		
County of London	448	517
Outer London	343	375
Other county boroughs	225	185
Other urban districts	276	216
Rural districts	154	163
Abroad or at sea	19	9
All places	1465	1465

TABLE III

Average Amount of Tobacco Smoked Daily over the Last Ten Years before Onset of the Present Illness Lung Carcinoma patients and Control Patients with Other Diseases

Disease Group	No of Non Smokers (a)	No Smoking Daily Average of <5 cigs (b)	5 cigs —	15 cigs —	25 cigs —	50 cigs +
Males						
Lung carcinoma patients (1357)	7 (0 5)	55 (4 0)	489 (36 0)	475 (35 0)	293 (21 6)	38 (2 8)
Control patients with other diseases (1357)	61 (4 5)	129 (9 5)	570 (42 0)	431 (31 8)	154 (11 3)	12 (0 9)
Females						
Lung carcinoma patients (108)	40 (37 0)	16 (14 8)	24 (22 2)	14 (13 0)	14 (13 0)	0
Control patients with other diseases (108)	59 (54 6)	25 (23 1)	18 (16 7)	6 (5 6)	0 (0 0)	0

Difference between proportions of light and heavy smokers
Men $\chi^2 = 93\ 77$, $n = 4$, $P < 0\ 000001$
Women (grouping together all who smoked 15 or more cigarettes a day) $\chi^2 = 14\ 36$, $n = 2$, $P < 0\ 001$

(a) A non smoker is defined as a person who has never smoked as much as one cigarette a day for as long as one year

(b) Ounces of tobacco have been expressed as being equivalent to so many cigarettes There is 1 ounce of tobacco in 26 5 normal size cigarettes, so that the conversion factor has been taken as 1 oz of tobacco a week = 4 cigarettes a day

control patients is shown in *Table III* From

heavy smokers (24 4 % and 13 0 % smoking 25 or more cigarettes a day against 12 2 % and 0 0 %) Moreover, the proportion of lung-carcinoma patients to control patients steadily increases as the amount of tobacco smoked increases The criterion used in *Table III* for the assessment of the amount smoked is the average amount of tobacco smoked daily over the 10 years before the onset of the patient's illness A number of other criteria were tested — the amount smoked immediately before the onset of the patient's illness, the maximum amount ever

in *Table III*

Evidence that these results cannot be interpreted as being due to the selection of specially light smokers to form the control group

TABLE IV

Most recent Amount of Tobacco Smoked regularly before the Onset of the Present Illness Lung carcinoma Patients and Control Patients with Other Diseases subdivided by Place and Date of Interview

Disease Group	Place and date of interview		Percentage of N S (a)	Percent smoking daily				No Interviewed
				1 cig (b)	5 cigs.—	15 cigs —	25 cigs —	
Carcinoma of Lung (men)	Greater London	1948 49	0 3	5 1	38 5	30 2	25 0	649
	Greater London	1950 51	1 0	3 3	38 2	31 4	26 1	306
	Bristol	1950 51	2 8	0 0	22 5	40 8	33 8	71
	Cambridge	1951	0 0	0 0	50 0	29 4	20 6	34
	Leeds	1950 51	0 0	1 9	47 2	34 0	17 0	53
	Newcastle	1950 51	0 0	2 1	37 3	39 3	21 3	244
	Whole Investigation		0 5	3 6	38 0	32 8	25 0	1357
Control Patients with Other Diseases (men)	Greater London	1948-49	4 2	8 5	45 1	29.3	12 9	649
	Greater London	1950 51	4 2	4 9	46 1	28 4	16 3	306
	Bristol	1950 51	4 2	2 8	49 3	28 2	15 5	71
	Cambridge	1951	2 9	8 8	52 9	29 4	5 9	34
	Leeds	1950 51	5 7	7 5	39 6	35 8	11 3	53
	Newcastle	1950 51	5 3	4 9	43 9	34 0	11 9	244
	Whole Investigation		4 5	6 7	45 3	30 1	13 4	1357
Carcinoma of Lung (women)	Greater London	1948 49	31 7	11 7	31 7	15 0	10 0	60
	Greater London	1950 51	25 0	15 0	20 0	10 0	30 0	20
	Bristol	1950 51	50 0	—	50 0	—	—	2
	Cambridge	1951	50 0	—	—	50 0	—	2
	Leeds	1950 51	20 0	20 0	60 0	—	—	5
	Newcastle	1950 51	68 4	15 8	15 8	—	—	19
	Whole Investigation		37 0	13 0	27 8	11 1	11 1	108
Control Patients with Other Diseases (women)	Greater London	1948 49	53 3	20 0	16 7	10 0	0 0	60
	Greater London	1950 51	55 0	10 0	20 0	10 0	5 0	20
	Bristol	1950 51	50 0	50 0	—	—	—	2
	Cambridge	1951	50 0	—	50 0	—	—	2
	Leeds	1950 51	60 0	—	40 0	—	—	5
	Newcastle	1950 51	57 9	15 8	26 3	—	—	19
	Whole Investigation		54 6	16 7	20 4	7 4	0 9	108

(a) See footnote to Table III
(b) See footnote to Table III

TABLE V

Age of Starting to Smoke, Number of Years Smoked and Number of Years stopped Smoking, Lung carcinoma Patients and Control Patients

Sex	Age at starting	Lung Carcinoma Pat. No	%	Control Patients No	%	No of Years Smoking	Lung Carcinoma Pat No	%	Control Patients No	%	No of Years Stopped	Lung Carcinoma Pat. No	%	Control Patients No	%
MEN	Under 20	1077	79 8	992	76.5	1—	12)	3 4	15)	6.2	0—	1280	94 8	1172	90 4
	20—	251	18 6	264	20 4	10—	34)		65)		1—	56	4 1	75	5 8
	30—	18)	1 6	33)	3 1	20—	746	55 3	725	55 9	10—	6)	1 0	6)	3 6
	40+	4)		7)		40+	558	41 3	491	37 9	20+	8)		23)	
	All ages	1350		1296		All periods	1350		1296		All periods	1350		1296	
	$\chi^2 = 7\ 95$, $n = 2$, $01 < P < 02$					$\chi = 12\ 66$, $n = 2$, $P < 01$					$= 25\ 87$, $n = 2$ $P < 001$				
WOMEN	Under 20	20	29 4	12	24 5	1—	14)	38 2	18)	53.1	0—	58	85 3	41	83 7
	20—	23	33 8	15	30 6	10—	12)		8)		1—	9	13 2	6	12 2
	30—	10)	36 8	7)	44 9	20—	36	52 9	20	40 8	10—	0)	1 5	0)	4 1
	40+	15)		15)		40+	6	8 8	3	6 1	20+	1)		2)	
	All ages	68		49		All periods	68		49		All periods	68		49	

has recently been obtained from some other workers who have conducted a survey of an *accurately* drawn random sample of the general population of Britain The questions asked were the same as those asked the patients in the present series and the results obtained, after correcting for *sex* and *age* and limiting the comparison to London, was that the sample of the general population *contained even* more non-smokers and less heavy smokers than the patients used for a control group in the present series It is hoped that it will be possible to get permission to publish the detailed results later

One reason for extending the investigation beyond the limits of the series reported earlier, was the desire to see whether the results *obtained in London could be confirmed in* other parts of England *Table IV* shows the results obtained in patients interviewed in five English towns and the new results obtained from patients in London hospitals compared with the results previously published The amount of tobacco smoked is shown as the most recent amount smoked (i e including the amount last smoked before stopping if the patient had stopped smoking) as that was the method of assessment used in the earlier publication It is seen that the results have been consistent throughout and in all the towns at which interviewing has taken place, except in the group of female lung-carcinoma patients interviewed at Newcastle In the Newcastle group the female *lung carcinoma patients are statistically* un- [illegible] from the female control pa- [illegible] ig habits [illegible] *r propor*tion of non-smokers The numbers of women with lung carcinoma interviewed at Bristol, Cambridge and Leeds are too few for separate assessment, grouped together the re- [illegible] with tho- [illegible] , *obtained* [illegible] ng simila rity throughout In none of the groups of control patients is the proportion of non smokers as low or the proportion of heavy smokers as high, as in any of the groups of lung-carcinoma patients

Table V shows a comparison between the lung-carcinoma and control patients with regard to the age at which smoking was begun the number of years smoking continued and *the number of years* it had been stopped All three comparisons show a significant diffe

TABLE VI

Proportion of Smokers who Inhale Lung-carcinoma and Control Patients

Disease Group	Percentage of Smokers Inhaling			No of smokers	No of non smokers	No of men interviewed
	Never	Occasionally	Regularly			
MALE						
Lung carcinoma patients						
Central growths	35 7	11 8	52 4	1066	6	1072
Origin uncertain	35 7	11 1	53 2	168	0	168
Peripheral growths	26 1	11.3	62 6	116	1	117
Total	34 9	11 7	53 4	1350	7	1357
MALE						
Control patients	32 6	11 0	56 4	1296	61	1357

rence between the male patients in the two groups, differences between the female patients are all in the same directions but are statistically not significant The lung carcinoma patients are seen to have begun smoking earlier to have continued longer and to have stopped if at all later The difference is the greatest in the last case, more than three times as many of the control patients as of

portion of smokers there was no greater ten

earlier observation — among 1,350 male lung carcinoma patients who had smoked, 34 9 % said they never inhaled, while among 1,296 male control patients the proportion was 32 6 % If, however, the lung carcinoma patients are separated according to the site of the growth it is found that only 26 1 % of the patients with peripheral growths never inhaled, while the proportion among patients with central growths was 35 7 % The dif-

TABLE VII

Proportion of Smokers who Smoke Pipes, Use Cigarette Holders or Smoke Filter tipped cigarettes Lung carcinoma and Control patients

Disease Group	Percentage of Smokers			No of smokers	No of Men interviewed
	Pure pipe	Pipe and cigarettes	Pure cigarettes		
MALE					
Lung carcinoma patients	3 9	21 7	74 4	1350	1357
Control patients	6 9	23 7	69 4	1296	1357
	Percentage of Cigarette Smokers using Holders			No of cigarette smokers	No of Men interviewed
MALE	Never	Occasionally	Regularly		
Lung carcinoma patients	95 0	3 0	2 0	504	523
Control patients	88 4	5 8	5 8	467	523
	Percentage of smokers smoking filter tipped cigarettes				
MALE	Never		Sometimes		
Lung carcinoma patients	99 4		0 6	504	523
Control patients	96 8		3 2	467	523

TABLE VIII

Average Amount of Tobacco Smoked Daily over Ten Years, divided according to Histological Type Lung carcinoma patients

Lung carcinoma patients	No of Non smokers	Average Amount Smoked Daily over ten years No Smoking				
		<5 cigs —	5 cigs —	15 cigs —	25 cigs —	50 cigs +
Adenocarcinoma	7* 3 9	3 2 3	9 14 1	16 13 1	7 8 6	1 1 0
Anaplastic, oat cell or squamous carcinoma	26 23 8	33 38 1	292 290 9	288 281 9	177 177 1	18 22 2
Histological type unclassified	1 5.9	10 6.3	41 40 7	4? 38 2	24 23 9	0 3 0
No histological confirmation	13 13 4	24 24 4	172 167 3	143 155.8	99 97 4	19 11 8

* The roman figures show the actual numbers observed those in bold are the numbers that would have *occurred if the group in question had had in each sex and at each age exactly the same smoking habits as* all the patients included in the table

The *relative importance of different methods* of smoking tobacco is illustrated in *Table VII* Pure pipe smokers are defined as persons who have never regularly smoked cigarettes for as long as one year and pure cigarette smokers as persons who have never *regularly smoked a pipe for as long as one* year The proportion of pure pipe smokers among all male smokers is lower in the lung carcinoma group than in the control group (3 9 % against 6 9 %) The proportions of *men who used a holder for smoking cigaret*tes and who had smoked filter tipped cigarettes are also shown in *Table VII* In both cases the proportions are lower in the lung carcinoma series (holders used 5 0 % against

TABLE IX.

Annual Death Rates from Lung Cancer per 1 000 Persons Living in Greater London by Age Group and Average Amount of Tobacco Smoked in Preceding Ten Years

Age	Non smoker	Average Amount Smoked Daily				
		<5 cigs	5 cigs —	15 cigs —	25 cigs —	50 cigs +
25	**0 005***	**0 03**	0 09	0 13	0 16	**0 52**
45	0 09	0 ?2	1 06	1 47	3 18	3 50
65 74	0 31	1 21	2.38	3 58	7 69	**10 24**

* Rates based on observation of less than five cases of carcinoma of the lung are given in bold

TABLE X.

Smoking Habits of Patients Living in Different Parts of the Country ;

*Divided according to Density of Population * (Men)*

Area of Residence	Percentage of Non smokers	Percentage Smoking Daily Average of					Percentage of			No of Patients Interviewed
		<5 cigs.	5 cigs.—	15 cigs —	25 cigs.—	50 cigs.+	Pure cigarette	Cigarette and pipe	Pure pipe	
Greater London	5 1	8 3	38 3	33 7	13 4	1 2	74 2	16 0	4 8	1393
County Borough	6 8	6 6	42 7	34 0	9 9	0 0	66.3	22 8	4 1	240
Other Urban District	8 4	13 3	37 1	32 3	8 7	0 2	59 9	23 9	7 8	439
Rural District	10 4	13 7	40 8	27 6	7 7	0 0	58 4	21 5	9 5	327

* In order to obtain evidence from greater numbers of men in rural districts and the smaller towns, 200 additional male patients in hospitals in a rural county of England were interviewed, the material is not included in other tables in the report

11 6 % ; filter-tipped cigarettes used, 0 6 % against 3 2 %) Questions about the use of cigarette holders and filter-tipped cigarettes were only included towards the end of the inquiry and the numbers of men interviewed are, therefore, smaller In each case the difference between the two groups is arithme-

lung-carcinoma would necessarily result in there being relatively few patients with lung-carcinoma who smoked a pipe, used a cigarette holder or smoked filter-tipped cigaret-

subdivision and conclusions about their protective value can only be extremely tentative Cigar smoking is too uncommon in Britain for any evidence with regard to it to have been obtained

of the whole series of lung-carcinoma patients The number of patients with adeno carcinoma is too small for any definite conclusions to be drawn one way or the other In the course of reviewing the diagnoses of

adenocarcinoma or as an adenoma The apparent difference between the results obtained by WYNDER and GRAHAM and those recorded in the present series may, perhaps, be

TABLE XI

Smoking Habits of Men and Women in Greater London

	Percentage of Non smokers	Percentage Smoking Daily Average of				
		<5 cigs	5 cigs —	15 cigs —	25 cigs —	50 cigs +
MEN	5 1	8 3	38 3	33 7	13 4	1 2
WOMEN	58 1	17 9	16 6	6 2	1 1	0 2

due to the use of different criteria for the diagnosis of adenocarcinoma

From the information obtained, it is possible to estimate the risks of dying of lung-carcinoma for each of the different levels of tobacco consumption Because of the different habits of smokers in different parts of the country and because the sample of patients interviewed cannot be taken to be representative of all England, it is preferable to limit the calculations to the information obtained about Londoners If it is then assumed that the Londoners with lung carcinoma who were interviewed were representative of the Londoners dying from lung carcinoma in 1950 and that the Londoners with other diseases who were interviewed were representative of all the inhabitants of London in 1950, the numbers of persons dying from lung cancer and the numbers of persons at risk can be calculated for each level of consumption of tobacco and hence death rates can be obtained The results are shown in *Table IX* and *Figure 1* It would appear that the risk increases steadily with age and with the amount smoked, so that the risk of dying of lung
an aver
is appro
about 33 times the risk for a non-smoker of the same age and 20 times the risk for a man smoking the same amount but 40 years younger

It has been referred to above that the amount habitually smoked is not the same in all parts of England and it is the general experience that women do not smoke as much as men It is natural to ask, therefore, whether these differences can account for the different death rates recorded in England for town and country and for men and women *Tables X* and *XI* show, in summary form, the different amounts of tobacco smoked by men living in Greater London, in larger and smaller towns and in the countryside, and by men and women living in Greater London For simplicity of comparison the results for men in different parts of England are shown for populations standardised for age according to the age distribution of the total male population of the country between the ages of 25 and 74 and the results for men and women are shown for populations standardised according to the age distribution of the total population of Greater London between the same age limits The results show a clear gradation from rural districts up to Greater London, both with regard to the amount smoked and to the proportion of cigarette smokers , they also show a very marked difference between men and women The differences do not, however, appear to be adequate to account for the difference in death rates recorded by the Registrar-General in different parts of the country

Similar calculations for men and women in Greater London are more in conformity with the Registrar-General's experience For example, on the basis of the rates given in *Table IX* and estimates of the numbers of non-smokers among men and women in Greater London, it is calculated that 145 deaths would have been expected among female non-smokers aged 25-74 in Greater London in 1950 against 8 deaths amongst the equivalent group of male non-smokers From the experience of the smoking habits of male and female cases analysed separately it is estimated that the actual numbers were approximately 146 and 6 The agreement with expectation, on the assumption that there is no sex difference in the incidence among non smo

ZUSAMMENFASSUNG

Die fruheren Untersuchungen, welche von Doll und *Bradford Hill 1950* veroffentlicht wurden, sind jetzt weitergefuhrt worden, sodass nun 1465 Falle von Lungenkarzinom erfasst *worden sind und ebenso* eine gleich grosse Anzahl von Kontrollpatienten mit anderen Krankheiten, wobei diese sorgfaltig ausge lesen wurden unter dem Gesichtspunkt gleiches Alter, Geschlecht, Zeitraum und, wenn moglich gleiches Spi*tal* Von den *1357 Mannern mit* Lungenkarzinom wa ren 7, d h 0,5 % Nichtraucher (Definition siehe Text) Von den 108 Frauen waren 40, d h 37,0 % Nichtraucher Die entsprechenden Zahlen unter den Kontrollpatienten betrugen 61 Manner (4,5 %) und 59 Frauen (54,6 %)

Von den Mannern mit Lungenkarzinom haben wah *rend der letzten 10 Jahre vor Beginn der Erkrankung* 24,4 % durchschnittlich 25 Zigaretten oder mehr pro Tag geraucht (oder gleich viel Pfeifentabak) Die ent sprechenden Zahlen fur die mannlichen Kontrollpatienten betrugen nur 12,2 % Bei den Frauen betru gen die entsprechenden Zahlen 13,0 % bei den Kar zinompatienten und 0,0 % bei den Kontrollen

Von 1350 mannlichen Lungenkarzinompatienten, welche rauchten, gaben 34,9 % an nie inhaliert zu haben, wahrend bei den Kontrollen die entsprechende Zahl 32,6 % betrug Wurden jedoch die Karzinom

Patienten mit zentralem Tumorsitz in 35,7 % der Fall war Dieser Unterschied ist statistisch signifikant Das ist moglicherweise so zu erklaren, dass der mit dem Tabakrauch vergesellschaftete karzinogene Faktor die Hauptbronchien erreicht, unabhangig davon, ob der Patient inhaliert *oder nicht*, dass aber das Inhalieren notwendig ist, damit er in die Bronchiolen gelangt

von mit uppe edri oder

ger bei Zigarettenrauchen, *Filterzigaretten* verwendeten

In all diesen Fallen war der Unterschied zwischen den beiden Gruppen arithmetisch signifikant, kann aber nicht unbedingt in dem Sinn interpretiert wer den, dass das Pfeifenrauchen oder das Zigaretten rauchen durch Halter oder Filter weniger Lungen karzinome zur Folge haben, als das gewohnliche Zi garettenrauchen, denn moglicherweise ist diese weni ger gebrauchliche Art zu rauchen immer verbunden mit nur geringem Rauchen In Bezug auf das Pfei fenrauchen scheint das indessen *keine* genugende Er klarung der Tatsachen abzugeben An Hand einer Tabelle zeigt der Verf die Wahrscheinlichkeit bei verschiedenen Alter und bei verschiedenen Tabakkon sum an Lungenkarzinom zu sterben

Es ist ganz offensichtlich, dass der *Tabak fur* die Patienten mit Lungenkarzinom einen atiologischen *Faktor darstellt* Es lasst sich noch nicht entscheiden, ob Tabakrauch *als alleiniger karzinogener Faktor* wirkt, oder ob andere Faktoren auch noch im Spiele sein mussen

SUMMARY

An earlier investigation by Doll and Bradford Hill published in 1950 has now *been extended so as to* comprise 1465 patients with carcinoma of the lung and an equal number of « matched control » patients with other diseases, each of these being carefully cho sen so as to be of the same age, the same sex, and *so far as possible in the same hospital, at the* same time as a lung carcinoma patient

Of the 1357 men with carcinoma of the lung 7, or 0,5 %, were non smokers (as defined in the text) Of the 108 women there were 40, or 37,0 % The corresponding figures for their paired controls were 61 men (4,5 %) and 59 women (54,6 %)

Of the *men with lung carcinoma* 24,4 % *reported* that they had been smoking over the last ten years before the onset of the present illness an average of 25 or more cigarettes a day (or the equivalent in pipe tobacco) The corresponding figure for the male con *trol patients was only 12,2 % For women these pro*portions were 13,0 % for the carcinoma group and 0,0 % for the control

Among 1350 male lung carcinoma patients who had smoked 34,9 % said they never inhaled while among 1296 male control patients the proportion was 32,6 % If, however, the lung carcinoma patients were sepa *rated according to the site of the growth it was found* that only 26,1 % of the patients with peripheral growths never inhaled, while the proportion among patients with central growths was 35,7 % The diffe rence is statistically significant A possible interpre *tation would be that the carcinogenic factor associated* with tobacco smoke reaches the main bronchi ir respective of whether the patient inhales, but that inhaling is necessary for it always to reach the bron chioles

The proportion of pure pipe smokers *among all* male smokers was lower in the lung carcinoma group than in the control group (3,9 % against 6,9 %), as were the proportions of smokers using holders for smoking cigarettes or smoking filter tipped cigarettes In each case the difference *between the two groups* was arithmetically significant, but could not neces *sarily be* interpreted to mean that smoking tobacco through pipes, cigarette holders, or filter tips is less likely to produce lung carcinoma than smoking ordi nary cigarettes in the ordinary way, *because it might* be that these less common ways of smoking tobacco are all associated with light smoking It did not ap pear, however, that this could be an adequate expla nation of the findings with regard to pipe smokers The author gives a table showing a *computation* of the risk of dying of lung carcinoma at various ages an

l factor

ing car

in

cinoma is strong Whether some other factor is also required to be present as well — so that tobacco smoke should be regarded as a co-carcinogen rather than as an independent carcinogen — cannot yet be determined

RESUMEN

Los primeros resultados de Doll y Bradford Hill que habían sido publicados en 1950 han sido completados actualmente por una encuesta que se refiere a 1 465 casos de canceres de pulmon y un numero igual de enfermos de otros procesos Cada uno de ellos ha sido cuidadosmanete seleccionado con el fin de ser de la misma edad, del mismo sexo y procedentes, a ser posible del mismo Hospital Entre los 1 357 enfermos afectos de cáncer pulmonar 7 o sea el 0,5 % eran no fumadores (como definido en el texto) Entre las 108 mujeres el porcentaje de no fumadoras era de 37,0 % o sea 40 casos Las cifras correspondientes de los testigos eran de 61 0 sea 4 5 % en los hombres y 59 mujeres o sea 54 6 % De los hombres con cancer de pulmon 24 4 % manifestaron que habian fumado por termino medio 25 cigarrillos por dia o una cantidad analoga de tabaco en el transcurso de los ultimos diez anos anteriores al comienzo de la enfermedad Las cifras homologas en los controles solo eran de un 12 2 % en los hombres en tanto que en las mujeres solo era de un 13 % para el grupo de cancerosa y de 0 % para los testigos

De los 1,350 canceres de pulmon que eran fumadores 34 9 % dijeron que no habian tragado nunca el humo mientras que esta proporcion era de un 32 6 por ciento en los 1 296 testigos Si se seleccionan los enfermos segun el asiento de la tumoracion parece evidente que de los enfermos en que el tumor era periferico 26 1 % tragaban el humo mientras que de los enfermos con tumor central esta proporcion solo era de un 35 7 % La diferencias es significativa desde el punto de vista estadistico Una interpretacion eventual seria la de que la substancia cancerigena asociada al humo del tabaco alcanza los grandes bronquios independientemente del hecho de tragar o no el humo mientras que el hecho de tragar el humo es absolutamente indispensable para que sean alcanza

análoga

Aun cuando en cada caso la diferencias entre los dos grupos sean aritmeticamente significativas no se puede concluir necesariamente que el hecho de fumar en pipa con boquilla o cigarrilos con boquilla filtro haga al enfermo menos susceptible al cancer de pulmon que al que fuma un cigarrillo ordinario por los medios corrientes Es posible que estos modos menos corrientes de fumar esten ligados al hecho de que el enfermo fume poco De todos modos parece que esta explicacion no es suficiente en cuanto a los fumadores

de pipa El autor expone un cuadro que expresa la probabilidad de muerte por cancer pulmonar en las

si la presencia de otros factores está requerida concomitantemente (el tabaco obrando como co carcinogeno mas que como agente cancerigeno independiente)

RESUME

Les premiers resultats de Doll et Bradford Hill qui avaient été publiés en 1950, ont actuellement été complétés par une enquête s'etendant à 1465 cas de cancers du poumon et un autre nombre egal de patients atteints d autres maladies Chacun d eux ayant ete soigneusement selectionné de façon à être du meme âge, du meme sexe et provenant, autant que possible du même hopital Parmi les 1357 patients atteints de cancer du poumon, 7 soit 0 5 % étaient non fumeurs (comme defini dans le texte) Parmi les 108 femmes, le pourcentage des non fumeurs etait de 37,0 %, soit 40 cas Les chiffres correspondants chez les contrôles etaient de 61 soit 4 5 % chez les hommes et 59 femmes soit 54 6 % Parmi les hommes presentant un cancer du poumon, 24 4 % ont signalé qu ils

de 12 2 % chez les hommes tandis que chez les femmes, ils n etaient que de 13 % pour le groupe de cancéreux et 0 % pour les contrôles

Parmi les 1350 cancers du poumon qui etaient des fumeurs, 34 9 % disaient ne jamais avoir inhale la fumee tandis que cette proportion etait de 32 6 % chez les 1296 controles Si l on selectionnait les patients suivant le siège de la tumeur il apparait que parmi les patients atteints de tumeur periphérique, 26,1 % inhalaient la fumee tandis que parmi les patients dont la tumeur etait centrale cette proportion n etait que de 35 7 % La difference est statistiquement significative Une interpretation eventuelle serait que la substance cancerigene associee a la fumee du tabac atteigne les bronches souches independemment du fait d inhaler ou non tandis que le fait d inhaler est absolument necessaire pour que soient atteintes les bronchioles La proportion de purs fumeurs de pipes était inferieure dans les cas de cancer du poumon à celle du groupe contrôle (3 9 % pour 6 9 %) La proportion des fumeurs utilisant des porte cigarettes et des cigarettes a bout filtre, avait la meme allure

Bien que dans chaque cas, les differences entre les deux groupes soient arithmetiquement significatives, on ne peut nécessairement conclure que le fait de fumer la pipe, d utiliser un porte-cigarette ou de cigarettes à bouts filtres rende le patient moins susceptible à faire un cancer du poumon que celui fumant la cigarette ordinaire par les moyens habituels,

il se pourrait que ces façons moins usuelles de fumer soient liées au fait que le patient fume peu. Il apparaît toutefois que cette explication ne semble pas suffisante en ce qui concerne les fumeurs de pipes. L'A. établit un tableau exprimant la probabilité de *mort par cancer du poumon aux différents âges, ceci* en fonction de la consommation de tabac. Il semble y avoir de sérieux arguments pour considérer le tabac comme un facteur étiologique dans une grande proportion de cancers du poumon. Il reste à démontrer si la présence d'autres facteurs est également requise (le tabac agissant comme co-carcinogène plutôt que comme agent cancérigène indépendant).

RIASSUNTO

I risultati di Doll e Bradford Hill pubblicati in un lavoro del 1950 sono stati adesso confermati e la casistica completata ed aumentata fino a raggiungere 1465 malati di cancro del polmone ed un numero corrispondente di ammalati di altre malattie. Particolare cura è stata presa onde ottenere una perfetta corrispondenza di età, sesso e provenienza dallo stesso ospedale. Dei 1357 uomini affetti da cancro del polmone 7 (pari al 0,5 %) non erano fumatori (secondo la definizione riportata nel testo). Delle 108 donne 40 (pari ad una percentuale del 37 %) non erano fumatrici. *Le cifre corrispondenti nella serie dei controlli* erano 61 uomini (4,5 %) e 59 donne (54,6 %).

Degli uomini affetti da cancro del polmone, il 24,4 % riferirono di avere fumato durante il decennio precedente l'inizio della malattia una media di 25 o più sigarette al giorno (oppure l'equivalente in tabacco da pipa). La cifra corrispondente nei controlli maschili era soltanto del 12,2 %. Per le donne il rapporto era di 13 % a 0 % nel gruppo dei cancerosi in confronto al 0 % nei controlli. Dei 1350 uomini malati di cancro del polmone « fumatori » il 34,9 % non aspirava, mentre nei 1296 controlli la proporzione era del 32,6 %. Suddividendo comunque i pazienti affetti da cancro del polmone, in base alla sede del tumore, si metteva in evidenza il fatto che solamente il 26,1 % dei malati con tumori periferici non aspiravano, *mentre la proporzione in malati con tumori* centrali era del 35,7 %. Questa differenza è statisticamente significativa. Una possibile interpretazione potrebbe essere che il fattore cancerigeno, associato col fumo di tabacco, raggiunga i bronchi principali indipendentemente dal fatto che il paziente aspiri o meno, ma che l'aspirazione del fumo sia sempre necessaria perchè i bronchioli vengano raggiunti e lesi. La proporzione di coloro che fumavano esclusivamente la pipa fra gli uomini era inferiore nel gruppo dei malati affetti da cancro del polmone che non nel corrispondente gruppo di controllo (3,9 % contro 6,9 %). La stessa proporzione si verificava nel caso dei fumatori di sigarette col filtro o che adoperavano il bocchino. Per quanto in ogni caso le differenze fra i *due gruppi fosse aritmeticamente significativo, non*

fuma normali sigarette in maniera normale, potrebbe darsi che queste abitudini meno comuni di fumare fossero legate al fatto che chi le adopera sia un modesto fumatore. Non sembra, *tuttavia*, che questa possa essere una spiegazione sufficente ed adeguata per quanto riguarda i fumatori di pipa. L'A. riporta una tabella in cui mette in evidenza il rischio di morire per cancro del polmone a seconda delle età ed in rapporto al consumo di tabacco. Che il tabacco sia un

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés.

Nous le regrettons et nous en excusons vivement.

La Rédaction

TOBACCO AND LUNG CANCER

BY

E. Cuyler HAMMOND and Daniel HORN

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To evaluate the role played by any environmental factor in the development of lung cancer is not easy It is now nearly twenty five years since the first controlled observations were attempted by LOMBARD and DOERING (3) in Massachusetts on the role of tobacco in cancer At that time the suggestive findings were on intraoral cancer — there were too few cases of bronchogenic carcinoma for analysis

When LOMBARD and his associates (4) repeated these observations a number of years later the number of cases of cancer of the respiratory system had increased to the point where they apparently found a statistically significant relationship of moderate size

Four major investigations which have used essentially the same method, have been reported within a relatively short time period

(1) SCHREK and others (5) reported on a group of veterans hospital cases
(2) LEVIN and other (2) reported on a group of cases from the Roswell Park Cancer Hospital
(3) WYNDER and GRAHAM (6) reported on a series of lung cases from a number of hospitals in several cities
(4) DOLL and HILL (1) reported on a series of cases in England

The method used, generally called the « historical » method, is this

(1) A number of cases with cancer of the

are determined
(2) A number of cases without cancer of the lung are also questioned and the proportion of non smokers light moderate and heavy smokers are also determined, and
(3) These two sets of proportions are compared to determine whether or not the proportion of smokers differs in the two groups

All of the studies cited have indicated a relationship between smoking and lung cancer, in that there is a higher proportion of smokers among the lung cancer cases than among the controls Why then are we continuing to study the relationship between smoking and lung cancer ? Unfortunately, although the historical method of approach has much to recommend it, it has a number of serious drawbacks

Altho gh the reported

ferences The apparent importance of tobacco varies in these studies from relative unimportance, of academic interest only, to an appearance of crucial importance and of major clinical interest

There are several statistical difficulties in the historical approach to this problem responsible for this disagreement First, although it is easy to define the lung cancer group, it is very difficult to define the so-

Un ted Stat

controlled studies the lung cancer and the control series have been matched with respect to sex and age There are, however, many selective factors

group

Furthermore when these cases are subdivided into several small subgroups, the proportions used to evaluate the results are based on small numbers in the denominators of the fractions As a result, it takes relatively little bias on the part of the interviewer or

TABLE I

Summary of Published Findings on Smoking Among Lung Cancer Patients

Bibliography Reference	Group	No of Cases	% of Non Smokers	% Smokers	% Cigarette Smokers
4	Ca of respiratory system	43	7 0	93 0	—
	Ca exclusive of respiratory and Buccal ca	715	20 6	79 4	—
	No cancer	1847	26 0	74 0	—
5	Ca of Lung	82	14 6	85 4	80 5
	Ca, exclusive of Lung, Larynx, Pharynx and Lip	[illegible]	23 9	76 1	59 2
2	Ca of Lung	236	15 3	84 7	66 1
	Other ca except Lip	506	17 1	82 9	48 0
	Lung non tumors	124	18 9	81 1	53 1
	Other non cancers	481	21 7	78 3	44 1
6	Ca of Lung	605	1 3	98 7	91 2
	Other Hospital Patients	780	14 6	85 4	65 2
1	Ca of Lung	649	0 3	99 7	95 1 (cigarettes only)*
	Non cancer Hospital Patients	649	4 2	95 8	88 3 (cigarettes only)*

* These include men who smoked both cigarettes and pipes as well as those smoking only cigarettes The *corresponding percentages for those smoking only cigarettes are 76 3 % in the cancer group and 70 6 %* in the control group

on the part of the patient who may have been told by his physician that smoking has caused his symptoms, to produce large fluctuations *in the data Careful studies of interviews by social scientists have demonstrated the re*markable extent to which interviews may be biased by the beliefs and attitudes of the interviewer, even when he makes every effort to be unbiased

For some time we have recognized that these objections may be overcome by using the follow up method of approach This consists of collecting information on smoking habits on a large population before the disease develops and then *following that entire population over a period of years* to determine the relative incidence of lung cancer in groups of people with various smoking habits In this way, problems of bias on the part of the collection of smoking histories are obviated, and *incidence rates are computed on the basis of* large populations so that random variations are of much less importance The follow up [illegible]

pensive procedure The primary advantage of the historical approach is the fact that it is a relatively inexpensive procedure for determining whether or not a scientific hunch is worth *further study* It is noteworthy that HILL whose results were among the most striking of all the historical studies has indicated his uncertainty in accepting the results at fa-

TABLE II

Summary of Published Findings on Smoking among Lung Cancer Patients

	Bibliography Reference	No	% Non Smokers	% Cigarette Smokers
Lung Cancer Series	(4)*	43	7 0	—
	(5)	82	14 6	80 5
	(2)	236	15 3	66 1
	(6)	605	1 3	91 2
	(1)	649	0 3	95 1
Control Series	(4)	715	20 6	—
	(4)	1847	26 0	—
	(3)	322	23 0	59 2
	(2)	666	17 1	48 0
	(2)	124	18 9	53 1
	(2)	481	1 7	44 1
	(6)	780	14 6	65 2
	(1)	649	4 2	88 3

* Refers to cancer of respiratory system All others in this group refer to lung cancer

ce value by having just inaugurated a follow-up study among British physicians on the effect of smoking

The disadvantage of the follow-up method of study is that it requires a great many years to accumulate the information or a tremendous number of cases or both It is estimated that at least 200,000 person years of exposure to risk would be required to arrive at an answer on the relationship between lung cancer and smoking, even if the study were restricted to white males between the ages of 50 and 69 In other words, 25,000 men would have to be followed for eight years or 50,000 men for four years, or 100 000 men for two years An even larger number of cases should be used for fully reliable results *Since interviews done by professional inter-*

questionnaires were designed and pre-tested in the field until a form was developed which proved to give reliable information in *the hands of volunteers*

The Society has a very large number of volunteer workers who in the past have made cancer dressings, distributed educational literature and raised funds These volunteers are now being used to collect the information on smoking habits Each volunteer researcher is being asked to obtain the smoking histories of about ten white men between the ages of 50 and 69 But the volunteer is only to see men she knows fairly well such as relatives, close friends and neighbors At yearly intervals thereafter each volunteer will report on her cases, but will only be asked if the man is dead or alive, and, if dead, the place and date of death The cause of death will be ascertained from death certificates Hospital and other medical records will be checked on all cases reported as dying of cancer or of any respiratory disease We hope that thoracic surgeons and pathologists will cooperate by supplying us with accurate information on such of their cases as are included in this study

DISCUSSION

Dr Levin How will you be notified of deaths in this survey ?

Dr Hammond The American Cancer Society has a division in every State and an office in every county where this study is taking place It has a paid staff who are in charge of collecting information The volunteer « researchists » who obtain the information each have substitutes in case they fall out for any reason Annually each volunteer must make a report on each case he has questioned — his present address, whether he has died and where etc In some states, e g New York and Michigan, the Health Department is cooperating and will check our names against their records of deaths

Dr Levin What will happen if a volunteer questioner drops out ?

Dr Hammond We have the whole hierarchy to help our Society's Divisional Office-area leaders — a group of people working on the survey in each town — with a group chairman Each individual who will be asking questions is known to us Then we have the independent check by Health Departments In some states Medical Societies are cooperating, or social insurance organisations or C I O union volunteers

DR LEVIN The question of bias in obtaining a smoking history from patients may be exaggerated For instance I have a table with ... patients ... lung and ... ig conditions other than tumours Both these show similar differences from the lung cancer group as do the non-lung control groups This suggests there has been no bias

On the question of the historical method and the long term forward study — both depend on obtaining answers to questions When the long term study has been going on for some time you may find that you have not asked the right questions We need the ... us the sort ... able in the ... utious with ... e snags we do not yet see

DR HAMMOND I agree I only said that I thought there was less likelihood of bias in the long term study One cause of bias which is now becoming evident is due to the great publicity which has been given to the dangers of tobacco smoking Many doctors now in U S A use a history of tobacco smoking as a diagnostic sign If they see an elderly person who has been a heavy smoker they automatically diagnose cancer of the lung Then when the patient dies they may not order a post-mortem and this kind of thing will lead to bias in our forward study I think we should only use histologically proved cases

Also have you considered that people may change their habits because of your questionnaire ?

DR HAMMOND This may happen, but Dr Doll has shown that it only happened to a very limited extent Nevertheless I agree that it is something we ought to watch for

DR SMITH If tobacco smoke is carcinogenic it must be a relatively weak carcinogen, for not every heavy smoker dies of cancer In the planning of statistical studies, I think it is important to consider experiences with weak carcinogens We have tested many such on mice in our laboratory Let me cite an example With relatively strong concentrations of a carcinogen, the tumour yields were closely related to the amount of exposure, but this relationship became erratic with the weaker concentrations Indeed, the 5 per cent. concentration evoked somewhat more tumours than did the 10 per cent If a statistician entered a world composed of mice exposed to weak carcinogens, that provoked tumours in only 10 to 5 per cent of animals, he would find great numbers of individuals who did not develop tumours for every one that did I submit that we may be entering exactly such a world when we try to compare lung tumour rates in individuals who are « moderate » as compared to « heavy » smokers The real control groups should be non smokers

DR HAMMOND Are you suggesting that the control group should never have been exposed to tobacco smoke ?

DR MAISIN This would not be possible in a civilized community I have never smoked, but look how I am exposed to tobacco smoke just now

... seem to go by households there is a familial tendency in fact

DR CLEMMESEN Has Dr Hammond any information on the incidence of lung cancer by occupation ? We have found rather high incidence of lung cancer and would suspect heavy smoking habits among journalists, architects and printers.

DR HAMMOND We have no information on this point but I suggest that this is the sort of information which should be collected for all countries

DR KORTEWEG With regard to the question of bias due to the existence of lung cancer Dr Doll s and Professor Bradford Hill s patients admitted as cases of lung cancer — but later found not to have the disease — gave the same answers as the control group This would suggest there has been no bias in the answers

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ZUSAMMENFASSUNG

Die Verff geben eine Darstellung der Methoden mit deren Hilfe der Einfluss des Tabaks auf die Entstehung der Lungenkrebse studiert werden kann und sie diskutieren insbesondere die histologischen Methoden und die wiederholten Nachkontrollen

SUMMARY

The authors give an evaluation of the methods available for studies on the influence of tobacco on the frequency of carcinoma of the lung and discuss particularly the historical method and the follow up method

RESUMEN

Los autores dan una apreciacion de los métodos utilizables en el estudio de la influencia del tabaco sobre la frecuencia del cancer del pulmon y comentan sobre todo los metodos histologicos y el de las observaciones repetidas en el tiempo

RESUME

Les Auteurs donnent une appreciation des methodes valables pour l'etude de l'influence du tabac sur la frequence du cancer du poumon et discutent plus particulierement les methodes histologiques et la methode des observations repetees dans le temps

RIASSUNTO

Gli A A prendono in esame i metodi per lo studio dell'azione del tabacco sulla frenquenza del carcinoma del polmone e discutono in modo particolare le ricerche istologiche e le indagini ripetute in epoche successive

Il nous a ete impossible, par suite de circonstances independantes de notre volonte de faire figurer la totalite des traductions des Résumés

Nous le regrettons et nous en excusons vivement

La Rédaction

PULMONARY TUMORS IN ANIMALS WITH PARTICULAR REFERENCE TO MICE ([1])

BY

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HISTORICAL NOTE

LIVINGOOD (37), during the course of some experiments on bacterial infections in 1896, discovered five spontaneous tumors in mice, one of which was a spontaneous pulmonary tumor, apparently the first to be reported in the literature This tumor was found in an albino mouse in which no other growths were noted, and LIVINGOOD believed it to be an adenocarcinoma arising within a bronchus During the period from 1905 to 1914 a large number of cases was reported and described in detail by HAALAND (16 17), TYZZER (68), MURRAY (51), JOBLING (31) and SLYE, HOLMES and WELLS (61) All of these pulmonary tumors were believed to be spontaneous in origin and primary in the lung although a number of them occurred in mice bearing tumors in other locations particularly in the breast They were variously diagnosed as adenoma papillary cystadenoma or adenocarcinoma TYZZER (68), and WELLS SLYE and HOLMES (61) observed growths which were thought to be epidermoid carcinomas With the exception of this latter type a reading of the descriptions and reference to the available illustrations strongly suggest the essential histologic similarity of most of them As to their point of origin there was no absolute agreement among the various authors although a great many were thought to arise from alveoli TYZZER (68) remarked on the resemblance of the tumor cells to bronchial epithelium but on the other hand noted in one instance that the tumor was small and completely independent of the bronchi By the use of serial sections JOBLING (31) thought

... owth to papilla- ... of a bronchiole ... literature was ... WELLS (61) ... rs might arise ... n the bronchial epithelium, although they admitted that it was extremely difficult to decide this point on the character of the tumor cells However, they believed that the papillary type of tumor arose more frequently from the alveoli Interest in these tumors apparently waned until 1925 when MURPHY and STURM (50) induced pulmonary tumors in mice by the repeated ... ar distillate ... the histolo ... illustrated a growth which was apparently identical with the type described by the earlier workers Their work was soon repeated by a number of investigators, most of whom simply referred to the induced tumors as pulmonary adenomas or adenocarcinomas With the establishment of the highly inbred A strain of albino mouse by STRONG (66) in 1921, a suitable test animal for the study of primary tumors of the lung became available BITTNER (6) reported on the spontaneous incidence of pulmonary tumors in this strain of mouse and ANDERVONT (1) showed that practically all young mice of this strain will develop multiple tumors of the lung within 2 ...

plants (1) of the ... hibit a spindle cell pattern which STEWART GRADY and ANDERVONT (65) demonstrated to be compatible with fibrosarcoma

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(1) Modified from an article submitted for publication in the Physio pathology of Cancer, edited by F Homberger and W Fishman, to be published by Paul B Hoeber, Inc, New York

With the exception of man and the mouse spontaneous tumors of the lung are rare in all species studied such as the horse the ox sheep cat rat kangaroo and fowl I have observed only a single spontaneous pulmonary tumor in a rat (29) although they have been induced in multiple form in this species by urethane (MOSTOFI and LARSEN (47)) The squamous metaplasia of bronchial epithelium in rats with bronchiectasis has frequently been mistakenly diagnosed as squamous carcinoma

Carcinogenic Agents and Methods of Induction

There are now a number of techniques for the successful induction of pulmonary tumors in mice In addition to tar and the carcinogenic hydrocarbons such diverse agents as nitrogen mustard (25) sulphur mustard (26) gamma radiation (41) and urethan (52) have all been shown to be carcinogenic One of the most potent of all carcinogens for lung tissue of mice is urethan administered parenterally or in the drinking water LARSEN (33) studied a number of related substances e g a series of homologous esters and a series of N alkylated derivatives of urethan and found none as active as ethyl carbamate Numerous other sedatives including ethyl alcohol the barbiturates chloral hydrate and paraldehyde have been tested and found to be negative Although pulmonary tumors almost never develop spontaneously in the rat they have been induced by urethan (47) by radioactive cerium (36) and by Beryllium (69)

The carcinogenic hydrocarbons and related chemicals have been successfully employed to induce pulmonary tumors in mice by various routes including cutaneous painting feeding and injection subcutaneously intravenously intraperitoneally intrapleurally and directly into pulmonary tissue The following compounds are carcinogenic for the lung of strain A mice following intravenous or subcutaneous injection 20 methylcholanthrene 1 2 5 6 dibenzanthracene 3 4 5 6 dibenzcarbazole 3 4 benzpyrene 15 16 benz dehydrocholanthrene 1 2 5 6 dibenzacridine 1 2 7 8 dibenzacridine 2 methyl 3 4 benzphenanthrene 4 methyl 3 4 benzpyrene and 2 amino 5 azotoluene In contrast the following compounds similarly tested have been shown to be noncarcinogenic 1 2 benzanthracene 3 methoxy 10 propyl 1 2 benzanthracene and colloidal thorium dioxide (3) A given hydrocarbon which is a potent carcinogen for the pulmonary tissue of mice may not show the same quantitative or qualitative carcinogenic activity when tested on other tissues as for example the subcutaneous or cutaneous tissue Indeed the potency of any given carcinogen to induce pulmonary tumors differs in mice of different strains The method of intravenous injection is one of the best ways to test exogenous pulmonary carcinogens Here the particle size is important for the larger the particles the more likely they

has been noted in the excretion rate of a carcinogen by resistant as compared with susceptible animals It is generally admitted that the pulmonary carcinogens act directly upon the pulmonary tissue in which there resides a potential neoplastic process as evidenced by the spontaneous incidence of these tumors It is believed that the carcinogens act by accelerating this inherent neoplastic tendency and that such acceleration is rapid and continuous following the single application of an agent With present methods of quantitative absorption spectrum analysis it is usually impossible to detect the presence of the carcinogenic hydrocarbon in pulmonary tissue later than one week following its administration (38)

The pulmonary tissue of mice of strains susceptible to spontaneous lung tumors is therefore a very sensitive test object for suspected carcinogens With this in mind LORENZ and STEWART (39) exposed strain A mice to the inhalation of tobacco smoke four hours a day for 12 months At the end of the experiment no increase in the occurrence of lung tumors was noted It is probable that in the presence of oxygen polycyclic hydrocarbons of known carcinogenic activity are not formed on the combustion of tobacco Recent reports including that of MILLS and PORTER (44) and others as given in the present Symposium suggest that the high incidence of pulmonary cancer in man is associated with excessive smoking of tobacco If true it has not been determined whether this is due to smoke *per se* (hardly likely in view of the experiments of LORENZ and STEWART (39)) or to the material which the smoker swallows

with the saliva during smoking or to other as yet unknown factors and mechanisms Whether the pulmonary tumor of the mouse can be induced by the same (at present unknown) carcinogens that cause human pulmonary tumors remains to be proved There is no experimental laboratory animal that develops spontaneous tumors of the lung identical with those common types that occur in man

Susceptibility of strains of mice

Among the various strains of inbred mice currently used in cancer research there is a pronounced difference in the incidence of spontaneous and induced pulmonary tumors Strain A mice have generally proved to have the highest incidence of spontaneously developed pulmonary tumors the figure being from 80 to 90 per cent in animals living 18 months or longer whereas strain L mice rarely develop this neoplasm SHIMKIN (60) tested seven strains of mice for their susceptibility to induction of primary pulmonary

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L were relatively resistant. The relative susceptibility to induction of primary pulmonary tumors was parallel to the susceptibility to spontaneous development of pulmonary tumors i e strains of mice having the highest incidence of spontaneous pulmonary tumors also showed the highest incidence of induced pulmonary tumors The pulmonary tumors induced in mice were alveologenic carcinoma There was no morphologic difference 1) between spontaneous and induced tumors 2) between tumors induced in the seven strains of mice 3) between tumors produced by methylcholanthrene and those produced by 1 2 5 6 dibenzanthracene 4) between tumors induced by different routes of injection (subcutaneous intravenous intratracheal) or 5) between tumors induced by the carcinogen in different states (in lard in horse serum as a cholesterol pellet or adsorbed on charcoal) GOWEN (10) found that like pulmonary tumors induced by the carcinogenic hydrocarbons the incidence of the urethan induced tumors depends upon the spontaneous incidence of these tumors in different strains of mice

GENETICS OF PULMONARY TUMORS IN MICE

The study of the genetics of pulmonary tumors has been greatly enhanced by the fact that the incidence of spontaneous pulmonary tumors in mice differs in different inbred strains (SHIMKIN 60 LAW 34 HESTON 18 19 LYNCH 43) Furthermore inbred mice having a high incidence of spontaneous pulmonary tumors are also more susceptible to the induction of these neoplasms by carcinogenic hydrocarbons Thus there is available experimental biological material of the utmost value for studies of pulmonary tumor genetics LYNCH (43) was the first to show that heredity as well as environment influenced susceptibility to the development of pulmonary tumors In an analysis of the susceptibility to induced pulmonary tumors HESTON (20 21) used two strains of mice namely strain A which is a high pulmonary tumor strain and Strain L which is a low pulmonary tumor strain By studying the F F, and backcross hybrid generations of mice receiving at 65 days of age an intravenous injection of 0 5 mgm of 1 2 5 6 dibenzanthracene he found that genetic factors as well as environmental factors are involved in the susceptibility to induced lung tumors The genetic factors influencing susceptibility are multiple in number and not due to one larger factor with modifying factors The minimum number of susceptibility factors by which strain A and strain L differ in this respect is four pairs and in all probability more In the F generation in this experiment HESTON estimated that 86 per cent of the susceptibility to pulmonary tumors depended upon genetic factors and 14 per cent to non genetic factors Susceptibility to induced pulmonary tumors has been shown to be associated with the chromosome carrying the genes 1) Shaker 2 and Waved 2 2) Flexed tail 3) Lethal Yellow and 4) Hairless Susceptibility to spontaneous pulmonary tumors is inherited in the same manner as that to the induced tumors and the two genes tested namely the lethal yellow and the hairless genes affect both in the same manner (22 23 24)

In order to determine whether genic action controlling the development of pulmonary tumors in mice is localized in the lung tissue or is manifested through some general systemic mechanism lung tissue from mice of strain A (highly susceptible to pulmonary

tumors) and from strain L (highly resistant to pulmonary tumors) was transplanted subcutaneously into a common host the F_1 hybrid of the two strains which then received an intravenous injection of dibenzanthracene (27) Pulmonary tumors developed in 39 1 percent of the transplants from strain A donors and in 3 6 percent of the transplants from strain L donors Thus in large part the difference in genetic susceptibility to pulmonary tumors in the donor strains of mice was retained in the transplanted tissue which suggests that the action of at least most of the susceptibility genes by which these two strains differ is localized in the lung tissue Proliferation of the bronchial epithelium occurred in the transplanted lung fragments particularly in these of the strain L mouse but this lesion was readily distinguishable from the neoplastic change

GROSS AND MICROSCOPIC APPEARANCE AND METASTASES OF ALVEOLOGENIC CARCINOMA OF THE MOUSE

The common pulmonary tumor (alveologenic carcinoma) of the mouse may be single

solitary but if multiple usually do not exceed four per animal The induced tumors are almost invariably multiple and both lungs may be extensively riddled with these growths LARSEN (personal communication) has frequently counted 100 and occasionally as many as 150 tumors per mouse treated with urethan Despite the fact that much of the lung tissue may be occupied by these multiple tumors osteoarthropathy has not been observed Indeed such mice show few if any clinical symptoms Both spontaneous and induced tumors are similar in appearance The tumors appear to grow expansively being surrounded by compressed pulmonary tissue but are unencapsulated They are therefore usually sharply circumscribed pearly white nodules often projecting slightly above the pleural surface of the lung Fresh or fixed material examined under the low power of a dissecting microscope gives a reasonably accurate index of the total number of tumors throughout the lung and inferentially of the potency of the carcinogen being tested In estimating the

number of lung tumors by the surface counting method it should be remembered that these lesions grow by expansion and that several closely adjacent tumors each of which is at first solitary eventually become confluent Thus instead of being counted as several they may easily be counted as one after they have fused This error is inherent in a [illegible]

time many adjacent tumors coalesce Surface counts therefore may be numerically lower after coalescence of tumors than if made earlier or if smaller doses or a less potent carcinogen are used

Microscopically spontaneous and induced tumors are similar most of them presenting a uniform picture of closely packed columns of cuboidal or columnar cells The cellular elements are supported by a sparse stroma of mature fibrous tissue containing small amounts of reticulum and collagenic fibrils Few blood vessels are present The cells of the tumor are arranged in acini showing papillary formation and the stromal pattern is similar to that of an epithelial growth The *cytoplasm of the tumor cells is generally* smooth slightly acidophilic and the free borders of the cells are devoid of cilia The nu[illegible]

not numerous Apparently two or more adjacent growths may coalesce as manifested by partial separation of the tumors and by minor differences of architectural pattern

That the pulmonary tumor of the mouse is a malignant neoplasm is evident from its lack of encapsulation its local invasiveness transplantability and ability to metastasize Although both lungs are often studded with multiple tumor growths it is my experience that metastasis is infrequent When metastasis does occur the secondary deposits may show sarcomatous characteristics WELLS SLYE and HOLMES (71) reported that of 147 132 mice coming to autopsy in Slye s laboratory where every mouse was permitted to live its full life span 2 865 mice (2 per cent) had spontaneous pulmonary tumors Of these cases 104 (3 6 per cent) showed

metastasis outside the lungs All showed metastasis in the mediastinal lymph nodes, many also showed growths along the chest wall and on the diaphragm Only 10 animals showed metastasis to other sites · 5 to the kidney 3 to the heart, 1 to the seminal vesicle, and 1 to the skull Of the 101 cases with metastasis, 33 of the metastatic growths showed more or less the structure of a sarcoma This was true even when no sarcomatous elements were identified in the primary growth Although in a number of primary lung tumors this sarcomatous structure was apparent, no primary sarcomas of the lung without epithelial elements were observed in these mice

Other types of pulmonary tumor

In addition to alveologenic carcinoma which is the common pulmonary tumor of the mouse two other histologic types of tumor have been induced Primary hemangioendothelioma of the lung has been induced by the subcutaneous injection of o-amino azotoluene(5) A squamous carcinoma has been induced by inserting directly into the lung (2) a piece of silk thread impregnated with 1,2,5 6-dibenzanthracene around which the neoplasm develops and may be bronchial in origin

LISCO and FINKEL (36) reported the occurrence of metaplastic changes in the bronchial epithelium and the development of malignant tumors therefrom in rats receiving radioactive cerium (Ce^{144}) administered as an aerosol into the lungs This is one of the few examples of the induction of squamous cell carcinoma in experimental animals

Induction of pulmonary tumors in embryo mice

It is noteworthy that the carcinogen urethan can pass the placental barrier and establish a carcinogenic process in the pulmonary tissue of embryo mice LARSEN reported a high incidence of pulmonary tumors in the offspring of mice injected intravenously with urethan during pregnancy In three day old mice the mothers of which had been treated with urethan during pregnancy, SMITH and ROUS (63) found cellular accumulations in the lung which were interpreted as the early stage of pulmonary cancer This is one of the few examples of the establishment of the carcinogenic process in tissues during embryonic life LARSEN (33) observed that the stage of pregnancy modifies the degree of the carci...

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jected during the final 24 hours of gestation exhibited fully five times as many pulmonary tumors as did mice whose mothers received the injection 2 to 5 days *ante partum* Much speculation has been stimulated regarding the significance of this phenomenon, but there are as yet no experimental data explaining its mechanism

Histogenesis of alveologenic carcinoma in the mouse

The early reports dealing with alveologenic carcinoma of the mouse variously classified this growth as adenoma, papillary cystadenoma or adenocarcinoma As to its exact point of origin there was no absolute agreement among the various authors although in some instances it was thought to arise from cells of the alveoli Others concluded that the tu-...

the observations of early workers some tumors appeared to involve alveoli only and their origin from alveolar cells was indubitable, other tumors involved both alveoli and bronchi, and hence the origin of these was not clear No tumors were described which involved bronchi alone and this constant involvement of the alveoli even though bronchi might also be involved made it seem improbable that these growths originated from bronchi The chief hindrances to the use of spontaneous pulmonary tumors in a study of histogenesis are their paucity and their slow development and evolution These obstacles are overcome by employing methods for the rapid induction of these neoplasms in large numbers in susceptible inbred mice by potent chemical carcinogens

Using such methods the histogenesis of these tumors was studied by GRADY and STEWART (15) using inbred strain A mice that are highly susceptible to induced lung tumors The animals were injected subcutaneously with 1,2,5,6 dibenzanthracene and 20-methylcholanthrene which induce multiple

exists, but the capillaries are contained in a ground substance with occasional so-called « alveolar » or « septal » cells, probably of mesenchymal o[illegible] that under certai[illegible] al-veoli have a [illegible] On the basis of [illegible] the study of the specificity of the germ layers, OPPENHEIMER (56) concludes that the doctrine of the absolute specificity of the germ layers must be abandoned The germ layers are probably capable under certain conditions of undergoing variations NEUBUERGER (53) concludes that the possibility of mesenchymal cells giving rise to a tumor with epithelial-like cellular elements cannot at present be rejected Whatever the final solution of this problem it is at present definite that tumors of alveolar origin can be induced in mice by appropriate experimental methods and that these tumors have the characteristic histologic pattern of papillary adenocarcinoma

TRANSPLANTATION STUDIES OF ALVEOLOGENIC CARCINOMA IN THE MOUSE

Alveologenic carcinoma the common primary pulmonary tumor of the mouse, which arises as a papillary adenomatous growth, often exhibits a sarcomatous pattern in its metastasis (71) The same change in histologic structure occurs when these tumors are transplanted serially to the subcutaneous tissue of mice of the same strain as the animal in which the primary tumor arise (4) This change from a glandular to a spindle-cell pattern on serial transplantation has been reported for other tumors, notably the mammary tumor of the mouse As might be expected, the report of this observation near the turn of the century occasioned considerable controversy among workers in the field of experimental oncology Many doubted the accuracy of the histologic diagnosis and there was and still is no satisfactory explanation for the mechanism of such change The observation that such a profound alteration in structure can occur was accepted with reluctance and reservation Many workers, although not denying the possibility still believed that the so-called « sarcomatous change » represents merely the occurrence of [illegible]

the observations of LUDFORD and BARLOW (42), who grew the transplant in tissue culture and reported the growth characteristics of sarcoma in vitro which had developed after transplanting a mammary carcinoma of a mouse This point was confirmed by STEWART, GRADY and ANDERVONT (65) who [illegible]

of many of the serially transplanted pulmonary tumors was indeed fibrosarcoma

The structural features of the transplanted tumors are on the whole uniform after they have become sarcomatous These growths are composed of plump bundles of elongated spindle cells which form interweaving and interlacing patterns The spindle-shaped tumor cells are usually large, with elongated darkly staining nuclei , mitotic figures are numerous The cytoplasm is drawn out into thin, unipolar or bipolar processes, which suggestively fuse with those of adjacent cells at their extremities The van Gieson and silver preparations reveal a pronounced increase in the amount of collagen and reticulum, as well as a profound change in the distribution of these intercellular fibers, when compared with the primary growths having an epithelial pattern The reticulum fibers form an extremely close [illegible] and in small [illegible]

matoxylin preparations, numerous fine fibroglia fibrils are associated with the tumor [illegible]

with this morphological [illegible] cult to consider them as being other than fibrosarcoma

The serial transplants of pulmonary tu[illegible] change, in [illegible] DER [illegible] tumor [illegible] and 21 neoplasms induced by 1,2,5,6-dibenzanthracene arising in strains A C, and C3H mice Hence, this sarcomatous change develops in transplants of both spontaneous and induced tumors and in different inbred strains of mice At the time of transplanta-

tion, each tumor was divided into two parts, one part was saved for histologic study and the other used for subcutaneous inoculation Several collateral lines were established At first, the tumors were transplanted every two to three months, but as the sarcomatous change developed the growth rate increased so that successive transplantations were made at three to four week intervals More than *one-half of the tumor series was carried on* for six generation transplants, and several others for more In the different specimens studied, all the various combinations of a papillary glandular carcinoma, solid carcinoma and sarcoma were observed, either intermingled with each other or with one or more pre-

in 5 lines the tumor transplant had become wholly sarcomatous in type, in 13 lines the tumor was composed of a combination of sarcomatous and carcinomatous structures, in 8 lines the glandular carcinoma type only was found, in 3 lines the solid carcinoma type, and in the remaining 8 lines combinations of glandular and solid carcinoma The tendency was for the glandular type of carcinoma to be replaced by the solid carcinoma type, and this in turn to be replaced by sarcoma The sarcomatous pattern often made its first appearance early in transplantation

The mechanism and underlying causes of the development of a sarcoma following serial transplantation of the primary pulmonary tumor of the mouse cannot be explained satisfactorily at present There are certain immediately obvious theoretical explanations which have been examined, but no definite conclusion has been reached The primary pulmonary tumor may possess a stroma which is

planation

A second possibility is that the stroma of the host undergoes malignant transformation If this is actually the mechanism of sarcoma development it is not to be explained on the basis of transfer of a known carcinogenic chemical, for this phenomenon has followed the transplantation of a spontaneous pulmonary tumor, and, furthermore, spectroscopic studies (LORENZ (38)) have shown

many of the transplanted tumors, have not yielded satisfactory indications that this stro-*mal reaction on the part of the host becomes* neoplastic

A third possibility is that the primary tumor cells undergo such fundamental alterations in their character as to become transformed into fibrosarcoma cells This possibility has been examined by STEWART, GRADY and ANDERVONT (65) in their transplantation experiments and, while the columnar and cuboidal cells of the tumor and elongated and spindle-shaped epithelial cells were sometimes intermingled with definitely sarcomatous areas, the observers could not definitely agree among themselves as to the significance of this relationship with the material studied However, this association may indeed be more than incidental

A fourth possibility that requires further exploration is that the primary pulmonary tumors are potentially mixed tumors to begin with The cell or cells from which they arise may possess potentialities like those of a synovial cell which, after undergoing a malignant change can grow as carcinoma or as sarcoma or as both The pulmonary tumor may possibly arise from two or more cell types There is much to recommend this line of speculation although the absence of direct proof precludes any positive deductions at present The so called endothelial tumors in man, as exemplified by the malignant syno

areas fibrosarcoma, and in still other areas

contained serosal cells from the pleura (an additional complicating factor) it would be

interesting to repeat this work using only deeply situated pulmonary tumors not in contact with the pleura

Pulmonary Adenomatosis

Pulmonary Adenomatosis in man (67) and animals is of interest because the histologic pattern of its lesion suggests that of the alveolar-cell carcinoma Although regarded by some as neoplastic in nature, other observers regard pulmonary adenomatosis as a reactive process in which the alveoli of the lung come to be lined by large epithelial cells The lesion in man is nearly a replica of that of an epi-

fectious nature is suspected The shepherds who tend the flocks of diseased animals have not been known to contract pulmonary adenomatosis as a result of their exposure to a possible microbiological agent in the sheep Somewhat similar pulmonary lesions to those of sheep have been described in horses, mules, guinea pigs and cats Serial roentgenologic

spread to other lobes of the same and of the opposite lung Grossly, the consolidated areas resemble the gray stage of lobar pneumonia, or they may appear as multiple nodules of varying size, widely scattered throughout both lungs If metastasis occurs, the lesion is considered to have been terminal bronchiolar carcinoma from the beginning rather than pulmonary adenomatosis Whether the lesions of terminal bronchiolar carcinoma and of pulmonary adenomatosis in man are one and the same condition or different and distinct processes is at present undecided Microscopically, the involved areas reveal pulmonary alveoli lined with a single layer of columnar or cuboidal epithelial cells containing mucus These cells do not show much variation in size, shape and staining capacity The origin of the epithelial cells lining the pulmonary alveoli of human beings affected by adenomatosis is a disputed question Such cells in adenomatosis may possibly be derived by proliferation of cells of the terminal bronchi, or they may have grown from a preexisting septal cell

A recent paper (28) placed on record two cases of pulmonary adenomatosis in untreated mice, one a virgin wild mouse and the other a male C3Hb mouse This paper referred to a previous one (40) reporting the occurrence of this pulmonary lesion in nine mice of the DBA Strain (some males, some females) ingesting olive oil emulsions containing 1,2,5,6-dibenzanthracene and 20 methylcholanthrene These lesions of pulmonary adenomatosis in the mouse were strikingly similar to those in man, in having the presence of a single layer of columnar cells lining the pulmonary alveoli The cytoplasm of each lining cell contained a large globule of mucus and papillary tufts of proliferating adenomatosis cells projected into the alveolar spaces in many places By contrast, the neoplastic cells of the common lung tumor of the mouse, alveologenic carcinoma, are all virtually devoid of mucoid material The opinion was expressed that the lesion of pulmonary adenomatosis in mice does not represent a malignant neoplastic process and certainly it is readily distinguished from alveologenic carcinoma in this species

Comparison of Pulmonary Tumors of Mouse and Man

There are many differences between the pathological characteristics of alveologenic carcinoma of the mouse and of bronchogenic carcinoma of man (13, 58, 72) In the mouse, the spontaneous tumor is often multiple, and arises from alveolar cells rather than from bronchial epithelium It exhibits an adenomatous pattern, whereas the majority of pulmonary tumors in man are squamous or undifferentiated carcinoma The tumors of mice show a predilection for the peripheral zones of the lung, are of low grade malignancy and are rarely fatal In man, on the other hand, pulmonary cancer arises in the region of the hilus and is invariably so highly malignant that it is rapidly fatal unless successfully treated in its early stage The metastases of untreated pulmonary cancer in man are usually widespread and exhibit a selective affinity for certain organs (e g brain and adrenal gland) in contrast to the tumor of the mouse which rarely metastasizes and, if

so, then not selectively to any organ site

The squamous cell type of pulmonary carcinoma of the mouse induced by inserting a dibenzanthracene-impregnated thread into the lung (2) differs from alveologenic carcinoma, the common spontaneous pulmonary tumor of the mouse and may prove to be quite comparable to bronchogenic carcinoma of man In their report of the induction of tumors in the lung of rats by radioactive cerium (Ce^{144}) administered as an aerosol LISCO and FINKEL (36) described the development of malignant tumors on the basis of metaplastic changes in the bronchial epithelium This experimental neoplasm in the rat may prove to be sufficiently similar to bronchogenic carcinoma in man to be used as a *suitable experimental test object* The transplantation of pieces of embryonic lung tissue along with a carcinogenic hydrocarbon into the subcutaneous tissue of adult mice of the same strain and induction of squamous cell and transitional cell carcinomas therefrom may also prove to be a valuable method for future study (63)

EXPERIMENTAL CARCINOGENESIS IN RELATION TO PULMONARY CANCER IN MAN

The increasingly important prominence of the lung cancer problem in man particularly from the point of view of it's probable progressive increase over the past several years, has created a demand for a suitable experimental tool for the study of possible carcinogens that are operative in man From the foregoing it is obvious that although a number of types of pulmonary cancer have been induced in experimental animals the disease as it occurs in man is not duplicated spontaneously in animals at least with any degree of frequency Squamous cell metaplasia occurs in animals deficient in Vitamin A and is often widespread in the lungs of old rats with chronic bronchiectasis, but primary bronchial carcinoma does not occur under these circumstances In searching for substances that are suspected of being carcinogenic for man the agents have been tested in a variety of ways in laboratory animals chiefly by inhalation skin painting and subcutaneous injection The problem of the etiology of lung cancer in man with special reference to the experimental aspects has been reviewed by SMITH (64) and much of the following is from his excellent article

Extracts of soot collected from the air in [illegible]

[illegible]

cutaneous injection in mice (35) The material collected from Pittsburgh, also caused a slight increase in lung tumors An increase of the incidence of pulmonary tumors occurred in mice exposed repeatedly to inhalation of soot collected from the air of an English city (45) and of sweepings from tarred English roads (9) It is noteworthy in this latter experiment that carcinoma of the skin occurred in some of the animals in the dust chambers In 1924 MOLLER (46) claimed to have found squamous cell carcinoma of the lung [illegible]

[illegible]

(54) exposed mice to repeated inhalations of asbestos dust Their claim that cancer was induced in 20 percent of the animals is likewise not concurred in by SMITH (64) Coal tar injected through the chest wall (14) into the lungs of rabbits and instilled intratracheally into the lungs of mice (7) failed to evoke cancer though the intratracheal method is said to have yielded an adenocarcinoma in a guinea pig (32) Methylcholanthrene in olive oil injected intratracheally into rats evoked sarcoma but not carcinoma (70) NISKANEN (55) claimed that he had observed squamous cell carcinoma in rat lungs after intratracheal injection of dibenzanthracene in olive oil According to SMITH (64) the photographs suggest that at least one lesion may have been neoplastic rather than merely me[illegible]

[illegible]

voked sarcomas and adenomatous tumors in lungs of mice but failed to elicit any other type of carcinoma (59) As mentioned earlier inhalation of tobacco smoke failed to increase the number of pulmonary tumors in the lungs of strain A mice over the spontaneous incidence although tars extracted from tobacco smoke have elicited cancer of the skin (12)

SMITH (64) points out that we are singu-

larly ill-equipped for the experimental study of one of the chief problems of human cancer namely lung cancer The common pulmonary tumor of mice alveologenic carcinoma has been the type of tumor most amenable to experimental study and as such it has occupied the attention of most investigators engaged in the study of lung tumors It has been pointed out however that this neoplasm represents a specialized situation with limited bearing on the types of tumors that account for the great majority of cases of lung cancer in human beings Carcinomas more nearly resembling those common in man have been produced from mouse lung by the tissue-transplant technic (64) Although this is an artificial procedure it can serve as pointed out by SMITH as a possible screening technic for testing substances suspected of having something to do with lung cancer Carcinomas have been induced in lung tissue removed from mouse embryos and implanted along with olive oil solutions of methylcholanthrene (62)

cell anaplastic and alveolar cell carcinomas and the neoplastic nature of each of these types of growths has been established by successful transplantation

SMITH (64) states that when the normal lymphatic drainage of the lung is disturbed as happens in the tissue transplant technic then solutions of carcinogens readily elicit carcinomas of various histologic types from the bronchial epithelium of the mouse These considerations may explain why carcinomas were obtained by ANDERVONT when he inserted into the lungs threads coated with dibenzanthracene for the chemical then existed as crystals and it has been presumed that some crystals were in direct contact with portions of the lining epithelium of bronchi In the plannin
reward
careful
which test materials are presented to the lungs Industrial physicians and hygienists are well aware that the particle size of noxious dust plays a large role in determining the site of tissue reaction in the lungs Thus the small particles in silicious dusts pass through the alveolar walls and exert their pathologic effects on the deeper tissues whereas the larger fibers of asbestos are arrested in the terminal air spaces and produce a wholly different pathologic picture According to SMITH (64) the known facts gleaned from experimental studies of silicosis and asbestosis may prove of much value in future inhalation studies of materials suspected to cause cancer of the lungs

DISCUSSION

DR LEVIN From Lorenz experiments it would seem that the potency of the agent we are concerned with is small The maximum incidence of lung cancer with the highest dosage of cigarettes was about 6 per cent In strains with pulmonary tumours there seems to be a difference between cigarettes and other forms of tobacco

DR STEWART We used cigarette tobacco We were concerned with the effect of smoking not particularly of cigarettes Lorenz thinks that there is a wide variation in the way people smoke — some people puff vigorously — others do not finish the cigarette they have started

DR MOORE Dr Evarts A Graham of St Louis is doing some work with dogs Cigarettes are smoked in machines and the deposit of smoke is painted on the dog s bronchus approached through a broncho fistula

DR SMITH I think we must distinguish carefully between direct painting of a tar

tempted to discuss this point in a review of experimental studies of lung cancer in the March (1952) issue of the Archives of Industrial Hygiene For example when carcinogenic hydrocarbons are injected via the trachea in solution in oil sarcomas result But Andervont obtained squamous cell carcinoma by introduction of crystals of dibenzanthracene When the vascular and lymphatic drainage of pulmonary tissue is destroyed as happens in the tissue transplant technique we have obtained a spectrum of carcinomas from the use of carcinogenic hydrocarbons either in oil or as crystals

One must further distinguish between re

sults obtained by testing carcinogens on the skin in contrast to pulmonary tissue Many years ago, Campbell swept up dust from tarred English roads and daily blew clouds of it into mouse cages The mice developed cancers on their skins, but in their lungs they developed adenomas, which are very different from the types of tumours found in the great majority of human cases of lung cancer

In the Lorenz smoking machine shown by Dr Stewart there is a distance of four to five feet between the bowl and the mouse cage Did Dr Stewart ever collect tar from the tube going from the bowl to the mice ?

DR STEWART Yes, Lorenz tested the tar It seems to me he obtained a sarcoma following subcutaneous injection of the carcinogen I agree with the criticism of comparisons made between mouse and human lung tumours This is a problem in comparative pathology For instance breast cancer in a mouse is quite different from breast cancer in a woman They are different histologically and in the course they take etc

DR MAISIN You have been showing that there was a genetic influence in the development of lung cancer in mice and that this influence was a local one Dr Smith has suggested that the tumours in the lungs of mice looked like the virus tumours in the breast. Does it influence the result if it is the father or the mother animal that has been affected ?

DR STEWART No

DR MAISIN May I remind you of the work of Fibiger and Moller who tarred rats on the back with the result that they developed tumours of the lung These tumours were of a benign nature

DR STEWART I believe that it has been shown that these were not true tumours but were lesions due to metaplasia of the bronchial epithelium

DR CLEMMESEN Yes Passey Leese and Knox have demonstrated in 1936 that Moller's rats must have suffered from vitamin-A deficiency *(Journ Path and Bact 42 425)*

DR SMITH While on the subject of experimental lung cancer I would mention that a German worker exposed mice to asbestos dust and described tumours in 20 per cent of the animals This figure, however, referred to only two animals One had an adenoma which is not uncommon in many strains of mice The other tumour was described as a squamous celled carcinoma, but the photograph resembles merely metaplasia Experimentally we are poorly equipped for the study of lung cancer I know no case of experimental production of epidermoid lung cancer in an animal by inhalation techniques except an experiment by Lisco at the Argonne Laboratory in Chicago, where epidermoid carcinoma was produced by radioactive cerium

DR HAMMOND I understand there is an infectious disease in sheep in South Africa and elsewhere which causes a lung lesion to alveolo-carcinoma

DR STEWART It is the lesion called Jaagdziekte Shepherds do not develop it, but it does occasionally occur in humans There is no compression of the blood vessels or invasion of the bronchi as occurs with a malignant tumour and there are metastases generally

DR MOORE I have seen one or two cases in man I agree it is not malignant It resembles alveolo carcinoma

DR STEWART We can distinguish it in mice from lung tumours by the mucus which the cells produce It may even project into a bronchus It is an investing sort of tumour

DR STEINER We should concede that we do not yet have the ideal experimental tumour to work with, but on the other hand some progress can be made with the material we have available

DR MAISIN Why not use acetylaminofluorene or urethane together with tobacco smoke ? It might also be interesting to examine the influence of tar inhalation with a view to the influence of tobacco smoke Maybe we should give it also in a way different from painting — for instance by feeding it

LADY KENNAWAY How would you make them eat ?

SIR ERNEST KENNAWAY When you obtained primary tumours in mice by painting them, what was the solvent used ?

DR MAISIN Benzene or aether

DR CLEMMESEN It has been suggested by Cobbett in 1917 that the tubercle bacillus

as tested with a different bacteria Particles of carcinogenic potency might be transferred to the bronchi in the same way

DR HAMMOND Dr Lombard has shown clinically the harmful effect of tobacco entering the lungs in the 1920es It was more pronounced with cigar and pipe smokers than with cigarette smokers

Could you not try painting the mouths of experimental animals with tar ?

DR STEWART The effect may be from the stem of the pipe rather than from what comes through the pipe Bakelite produces sarcomas in rats so the harmful effect may come from the stem of the pipe and not from the tobacco

DR STEINER What you are calling adenomatosis is included in Dr H Gideon Wells type E preadenomatous hyperplasia Some of these conditions which he called type E preadenomatous hyperplasia you call *adenomatosis*

DR STEWART That is interesting I would like to look that up

DR STEINER I believe I am justified in making that comment It is my own conclusion from examining his material

DR STEWART Have you seen any cases of pulmonary adenomatosis ?

DR STEINER I have but I have not called it that

DR CLEMMESEN We are paying a great deal of attention to the chemical constitution of factors but there may also be physical factors at work For instance the size of the particles in smoke inhaled for instance from a Diesel autobus might be of importance

DR STEWART Particle size plays a role in lung t
venously
the capil
large the
produce lung tumours

DR MAISIN Solubility must play a role

May I ask Dr Moore if in the recent experiments done in St Louis Professor Graham has been able to induce tumours on bronchi exposed to tar ?

DR MOORE In about two years painting once a month he produced what appeared to be one small papilloma in the bronchus of a dog Dogs must be more resistant to carcinogens

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ZUSAMMENFASSUNG

Der Verf gibt einen geschichtlichen Ueberblick uber die Lungentumoren bei Versuchstieren, er bespricht die verschiedenen karzinogenen Stoffe die Empfindlichkeit der einzelnen Mausestamme und deren genetischen Aspekte Er beschreibt die makroskopischen und mikroskopischen Bilder des alveolaren Karzinoms der Maus und deren Metastasen ebenso werden auch die anderen Lungentumorformen besprochen Dann werden die Methoden der Tumorerzeugung bei Mauseembryonen behandelt Ausserdem wird ein Ueberblick gegeben uber die Untersuchungen der Histogenese der alveolaren Mausekarzinome und deren Transplantationen Dann folgt eine Besprechung der Lungen Adenomatose und ein Vergleich der Lungentumoren bei Mausen und Menschen Der Verf schliesst mit dem Versuch diese experimentell gewonnenen Resultate auf die experimentelle Lungenkarzinomerzeugung beim Menschen zu übertragen

SUMMARY

The author gives a survey of the history of lung tumors in experimental animals He reviews the various carcinogenic agents and the susceptibility of various strains of mice and its genetic aspects He gives a description of the gross and microscopical appearance of alveologenic carcinoma in the mouse and its metastases as well as a review of other types of lung tumors The induction of pulmonary tumors in embryo mice is reviewed Furthermore the author gives a survey of investigations on the histogenesis of alveologenic carcinoma in mice and reviews transplantation studies of this disease There follows a discussion of pulmonary adenomatoses and a comparison of pulmonary tumors in mouse and man The author ends with application of our experience with regard to experimental carcinogenesis on pulmonary tumors in man

RESUMEN

El autor hace la historia del cancer del pulmón en los animales de experimentacion y pasa revista a los agentes cancerigenos y a la predisposicion al cáncer de determinadas cepas de ratones y a sus aspectos geneticos

El autor hace la descripcion macro y microscópica

de los cánceres de origen alveolar en el ratón y de la evolución de sus metástasis Revisa tambien todo el grupo de los otros tipos de tumores pulmonares y hace una recapitulación de los métodos de provocación de cánceres de pulmón en el embrión de ratón Resume luego las investigaciones realizadas sobre la histogénesis y la genesis de los carcinomas alveolares del ratón y prevé la posibilidad de transplantar esta lesión Discute las adenomatosis pulmonares y hace una comparación entre un tumor del pulmón en el hombre y el ratón

El autor termina tratando de expresar los resultados experimentales en función de la carcinogénesis pulmonar en el hombre

RESUME

L'A fait un historique du cancer du poumon chez des animaux d'expérience, il passe en revue les agents cancérigènes et la prédisposition au cancer de certaines souches de souris et leurs aspects génétiques

L'A fait la description macroscopique et microscopique des cancers d'origine alvéolaire chez la souris et de l'évolution de leurs métastases Il revoit encore tout le groupe des autres types de tumeurs du poumon L'A fait une recapitulation des méthodes d'induction de cancers du pommon chez l'embryon de souris L'A résume ensuite les recherches faites sur l'histogenèse des carcinomes d'origine alvéolaire chez la souris et envisage les transplantations de cette tumeur L'A discute les adénomatoses pulmonaires et fait une comparaison entre une tumeur du poumon chez l'homme et chez la souris

L'A termine en essayant d'exprimer les résultats expérimentaux en fonction de la carcinogenèse pulmonaire chez l'homme

RIASSUNTO

L'A dopo aver premesso le notizie storiche sul cancro del polmone negli animali da esperimento, l'A passa in rassegna gli agenti cancerigeni e prende in esame il problema della predisposizione ad ammalarsi di cancro dei diversi tipi di topi ed i loro aspetti genetici L A descrive dal punto di vista macro e microscopico i cancri di origine alveolare nei topi e delle loro metastasi, come pure passa in rivista tutti gli altri tipi di cancro del polmone Inoltre l'A riferisce brevemente i metodi di induzione del cancro del polmone negli embrioni di topo e quindi fa un riassunto delle ricerche eseguite sulla istogenesi del carcinoma alveolare nei topi ed espone i metodi di trapianto di questo tumore Segue una disamina sulle adenomatosi polmonari ed uno studio comparativo sui tumori polmonari nell'uomo e nel topo L'A termina il suo lavoro tentando di interpretare i risultati sperimentali ottenuti in funzione della carcinogenesi polmonare nell'uomo

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés

Nous le regrettons et nous en excusons vivement

La Rédaction

SOME REMARKS ON THE AGE CURVE IN LUNG CANCER

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R KORTEWEG
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Graphs which give the variations with age of death rate from cancer may be regarded as expressing the susceptibility to cancer, postponed by a few years The shape of the so-called age curve for cancer of the lung is just what would be expected if its real shape was similar to the shape of other exogenous cancers and if lung cancer, moreover, had increased at the same rate as mortality statistics seem to suggest Its shape gives evidence regarding the course of the endemiology of lung cancer in the past years From the shape of this curve it must be possible to gain an impression of the size of the increase in countries where figures for lung cancer deaths for previous years are not known (*Brit J Cancer*, 5 21, 1951)

The age curve for incidence of cancer of the respiratory tract in males given in the booklet Cancer Illness Among Residents of Chicago, Illinois Morbidity Series 6, 1952, does not show a decrease at high age For the construction of this age curve age groups of 35 to 44, 45 to 64, and 65 and over were used If for England and Wales this age curve is constructed with similar age groups, the decrease at high age is also lost The shape of the Chicago age curve, therefore, does not plead against the possibility that in Chicago lung cancer might be on the increase The same holds true for the age curve of cancer of the respiratory tract, with its steep ascent at high age, in Vienna, where large age groups were also used

[illegible] of this [illegible] It is [illegible] in ac- [illegible] of the Registrar General's Statistical Review of England and Wales for the six years 1940 to 1945 Text, vol I Medical (i e 0-34, 35-44, 45-54 55-64 65-74 75 and over)

The shape of the age curve in lung cancer shows us that after the increase at lower age has come to an end, it will still continue for the higher age groups The greater part of this increase of lung cancer mortality, therefore, will concern persons more than 60 years of age, which is about the upper limit for operability for lung cancer In the future the percentage of curability in lung cancer — which at this moment is distressingly low (no more than about four per cent) — may therefore still decrease considerably

DISCUSSION

DR CLEMMESEN I would like to express my appreciation of the method which Dr Korteweg has introduced We are going to adopt it as much as we can It is of course applicable to other cancers as well as of the lung, but we would prefer quinquennial age groups (cf recommendation 2)

DR LEVIN Dr Korteweg is to be congratulated on having made these observations The cohort method was first used in tuberculosis studies by Frost in the United States and by someone before him in Germany *) [illegible]

in lung cancer, from annual age-specific rates One might take exception to Dr Korteweg's characterization of one curve as the « real one » Both curves are real The age curve at a given time is a resultant of at least two influences a) That due to age alone, b) that due to the date of birth, assuming such an influence exists The age curve for a cohort holds the latter influence constant

(*) Editor's note Perhaps R Korteweg Über die Epidemiologie der Tuberkulose Z Tuberk 49 191, 192[illegible]

This accounts for the fact that in the latter curve lung cancer shows the constant increase with age *characteristic of most forms of* human cancer A suggested implication of Dr Korteweg's observation is that, in looking for environmental factors for lung cancer, we should look for one which is progressively stronger in persons born in more recent years Our data from New York State indicate *that cigarette smoking* fulfills this condition Perhaps there are other such factors which we should look for and test for

Dr Korteweg Maybe benzpyrene in the atmosphere is just as important working as an initiater

Dr Levin No, I do not entirely agree Something in the air to which everyone is exposed does not fill the bill unless you can find something to which people born in 1910 were exposed to a greater extent than people born in 1890

ZUSAMMENFASSUNG

Es ist manchmal nützlich die Karzinomfälle zu analysieren indem man sie in Gruppen einteilt z B in gleichaltrige Fälle Auf die Lungenkarzinomfälle angewandt ergibt diese Methode, dass diese Gruppen von Menschen mit zunehmendem Alter eine zunehmende *Krebshäufigkeit analog der Altersverteilung* anderer Karzinome aufweisen während die Altersverteilung des Gesamtmaterials eines Landes oder einer Stadt einen Gipfelpunkt aufweist z B bei 55 Jahren

SUMMARY

It is sometimes a useful procedure to analyze a material of cases of cancer dating *from a period of* some length by subdivision into cohorts i e groups of persons born in the same year When applied to a material of cases of cancer of the lung this method will reveal that while the distribution by age of the total material from a country or a town may show a peak for instance at the 55th year of age, the cohorts will *show a gradual increase in frequency* with age, analogous to the distribution by age of other cancers

RESUMEN

A veces es útil analizar los casos de cancer que datan de varios anos subdividiéndoles en *grupos de* personas de la misma edad «cohortes» Este metodo aplicado a los casos de cancer de pulmon revela que por una parte la distribución segun la edad de todos los casos de una comarca o de una ciudad pueden mostrar momentaneamente un maximo de frecuencia a los 55 años de edad, los «cohortes» muestra un aumento progresivo de frecuencia en funcion de la edad analoga a la observada en otros cánceres

RESUME

Il est parfois utile d'analyser les cas de cancer remontant à plusieurs années en les subdivisant en «cohorts», soit par groupes de personnes du même âge Cette methode appliquée aux cas de cancers du *poumon revele que d'une part* la distribution suivant l'age de tous les cas d'une contree ou d'une ville peut montrer momentanement un maximum d'incidence à 55 ans, les «cohorts» montrent une augmentation progressive de frequence en fonction de l'age analogue à celle observée pour d'autres cancers

RIASSUNTO

E cosa utile analizzare a volte la casistica dei cancerosi di vecchia data suddividendola in gruppi di persone della stessa eta Questo sistema applicato nei casi di cancero del polmone puo a volte mettere in evidenza il fatto che mentre la distribuzione per eta di tutti i casi di una citta o di una provincia può raggiungere un massimo di frequenza a 55 anni la suddivisione dei soggetti in gruppi di soggetti della stessa eta ci mosterà un aumento graduale di frequenza con l'eta analogo alla distribuzione per eta delle altre forme di cancero

THE OCCURRENCE OF LUNG CANCER IN MAN

BY

Morton L. LEVIN

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Epidemiology is traditionally defined as the study of outbreaks of unusual frequency of

miology — essentially the comparison of affected with unaffected groups in the population — are applicable to endemic as well as epidemic disease the term *epidemiology* is often used in the United States to indicate the use of the epidemiologic method whether applied to endemic or epidemic disease Since some forms of human cancer including lung cancer occur with higher than normal frequency in certain segments of the population there may be some point in retaining both terms — epidemiology and endemiology — for the study of the incidence of cancer in man [1] Perhaps we need also some more general term — such as *demiology* — to indicate the synthesis of knowledge regarding the « normal » occurrence of a disease in the general population and its higher (or lower) than normal occurrence in sub-groups of that population [2]

Lung cancer is of particular interest because its recorded increase during the past 20 years in the United States the United Kingdom and in several other countries is greater than that of any other form of cancer An important question is whether this increase is real If not real it would follow

determined by hereditary factors or by constant environmental factors Since a spontaneous genetic mutation affecting large numbers of human individuals at the same time has never been observed a real increase in lung cancer incidence would mean that some environmental factor or factors acting directly on the lungs or indirectly by inducing genetic mutations in a large number of individuals must be looked for

A notable feature of the observed increase in lung cancer mortality and incidence is the greater *rate of increase* among males (see *Table I*) In New York State the age standardized mortality between 1930 and 1950 increased among males by 385 per cent among females by 68 per cent In contrast age adjusted mortality from all other sites of cancer increased only slightly among males and decreased by 15 per cent among females The data for the United States white population are not strictly comparable, however they also show a considerably greater increase in lung cancer in males If the increase in lung cancer mortality were due entirely to improved diagnosis we would have to postulate either (a) that from 1930 to 1950 diagnostic accuracy had increased more than five times

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(1) A precise definition of epidemic is difficult What is called an epidemic depends on what is considered unusual incidence We may ask unusual with respect to what? Incidence may be unusual for a certain age group sex social class geographic area occupational group season or period The « usual » or « normal » incidence of typhoid fever in 1900 would certainly be considered an epidemic today The ordinary concept of an epidemic is that of an outbreak which begins reaches a peak and subsides within a short period — usually less than 12 months This concept is based on the natural history of infectious diseases most of which have short incubation periods For a disease with a long « incubation » period, such as cancer the epidemic period may well be 0 or 30

ncreasing freque cy and has not yet reached its peak or plateau

(2) Editor's note The term endemiology of cancer was adopted by the Symposium in Oxford 1950 in accordance with Webster's definition of the term endemic which if applied to a disease will mean regularly occurring in or pertaining to a certain population or region This definition seems to provide the term endemic occurrence for a disease occurring regularly as most cancers do

TABLE I

Increase in Mortality from Cancer of Lung and other Sites — New York State and United States Males and Females

	Cancer	Deaths per 100,000 living Males		Females		Per cent change	
		1931-33	1948 50	1931-33	1948 50	Males	Females
N Y State*	Lung	4 7	22 8	2 5	4 2	+ 385	+ 68
	Other Sites	110 3	112 7	151 2	128.8	+ 2	— 15
		1930	1945	1930	1945		
United States** (white)	Lung	3 0	13.9	1 8	4 4	+ 363	+ 144
	Other Sites	89 6	114 8	110 7	130 9	+ 30	+ 18

* Exclusive of New York City, age adjusted to 1940 population, New York State

** Not age adjusted Includes lung, bronchus, pleura, trachea, and «unspecified sites of respiratory system» Source Cancer Mortality in the United States (3)

as much in males as in females, or (b) that, in 1930, diagnosis was five times as accurate in females as in males There are no facts to support either postulate A more reasonable conclusion would seem to be that a real increase in lung cancer has occurred, at least in males, and possibly also in females The extent of this real increase cannot be determined accurately If we were to assume that *all* the increase among females is diagnostic and that this increase measures the extent to which improved diagnosis contributes to the recorded increase, one might infer that the real increase in lung cancer mortality among males in New York State has been of the order of 385 68 = 317 per cent, or about 15 per cent per year

Lung Cancer Increase by Age

The recorded increase in lung cancer has not been the same at all ages As will be seen in *Table 2*, the increase between 1930 and 1950, among males, was greatest at ages 55 to 69, in New York State and the United Kingdom The United States data show two «peaks» of increase — at ages 55-59 and 75-84 However, *in all three sets of figures* the increase in the oldest age group is less than in the preceding age group

In females *(Table 3)*, the greatest increase occurred, in New York State and the United Kingdom, in the oldest age group, 75 years and over *The United States data* which are available for two older age groups, indicate that the 75 84-year is the age group of greatest increase

These age differences in the recorded increase of lung cancer also are difficult to re

improvement would vary markedly with the age of the patient

Both the sex and the age differences in the recorded increase in lung cancer mortality indicate that this increase is not readily explainable by changes in diagnostic accuracy A real increase in incidence of lung cancer cannot be excluded and appears to be the more reasonable explanation of the observed facts

Lung Cancer in Cohorts

An interesting feature of the annual age specific mortality rates for lung cancer is their decrease in older ages, which gives the mortality curve a peak KORTEWEG (8) has shown that when the age-specific rates for England and Wales are rearranged by cohorts ([3]) (persons born in the same year or

(3) The term «cohort» for persons born the same year (or group of years) is that used by W H Frost in his analysis of tuberculosis mortality (7)

In this paper, Frost notes that a previous analysis of tuberculosis mortality by cohorts was made by K F Andvord (What can we Learn by Studying Tuberculosis by Generations? Norsk Magasin for Laegevidenskaben — *91 642 660, June*, 1930)

Editor cf Korteweg Z Tuberk 49 191 1927

TABLE II

Lung Cancer Mortality per Million Living

MALES

Age	United States		% Increase	England and Wales			N. Y. State		
	1930	1945		1931-35	1945-49	% Increase	1931 33	1948-50	% Increase
35 44	27	69	156	68	168	147	27	74	174
45 54	73	258	253	215	700	226	106	394	272
55 64	124	568	358	346	1412	308	176	996	466
65 74	153	599	292	344	1436	323	157	1218	676
75 +				235	844	259	129	868	573
75 84	94	456	385						
85 +	89	269	202						
All ages	31	132	326				47*	228*	385

* Age adjusted to 1940 population, New York State

group of years), the rates do not decline in the older years, but, instead, continue to increase with age The data for New York State show the same phenomena *(Graph 1)* (It is of interest that cancer of the ovary exhibits a similar relationship)

In *Graph 1*, the age-specific rates for successive cohorts approximate straight lines, indicating a constant rate of increase with age It is tempting, but probably dangerous, to project these lines, so as to estimate mortality in the next decade (The data for the United Kingdom indicates that the cohort age-specific rates tend to curve to the right ,

TABLE III

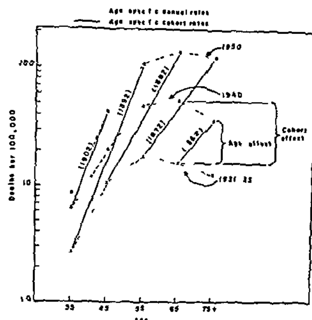
Lung Cancer Mortality per Million Living

FEMALES

Age	United States		% Increase	England and Wales			N Y. State		
	1930	1945		1931 35	1945-49	% Increase	1931 33	1948 50	% Increase
35-44	15	27	80	18	36	100	16	18	12
45 54	32	66	106	46	94	104	37	55	49
55 64	79	145	83	92	196	109	100	129	29
65 74	100	301	201	123	307	150	112	241	115
75 +				104	275	164	53	304	474
75 84	71	226	218						
85 +	53	131	147						
All ages	18	42	133				25	42	68

GRAPH I

LUNG CANCER MORTALITY
NEW YORK STATE
MALES



in other words, the rate of increase is not constant) However, even a conservative projection of these cohortal rates predicts a marked increase in lung cancer within the next decade

Analysis of the cohortal age-specific rates and their relationship to the peaks of the age-specific annual rates reveals that the latter are due to changes in relation of two values, that due to the cohort and that due to age The change (in this case, an increase) in rate, at the same age, between two cohorts separated by a given period (in this case, ten years) may be termed the « cohort effect » The increase in rate, in the same cohort, between two age groups (separated by the same period) may be termed the « age effect » A peak occurs in the annual curve when the cohort effect, at that age, exceeds the age effect for the preceding cohort For example, in *Graph I*, the age-effect of the ten years from age 65 to 75 is less, for the 1862 cohort, than the cohort effect at age 65, between the 1862 and the 1872 cohorts This accounts for the peak at age 65-74 in the 1940 annual age-specific curve The 1872 cohort again shows the excess cohort effect, in the 1931-33 curve It may be a coincidence that standardized machine-made cigarettes first became available in the United States in 1877

Lung Cancer and Smoking

Many
tionship
ADLER (

plastic Diseases » (6), summarized as follows « It would appear that cancer of the lung causes between 5 and 10 per cent of all *cancer deaths*, *that in spite of the absence of* statistical proof, the impression of most clinicians should be accepted that the disease has increased markedly in the past two decades, from 1920 to 1940 , and that abundant cause for this increase may probably be found in the increased exposure to many *forms of irritating inhalations, among which* tobacco, coal tar products, and dusts of many kinds figure most prominently »

For the most part, the observations linking lung cancer with the use of tobacco have been based on data which were not considered definitive More recent studies (10, 2, 5) have *been well designed and have left little doubt* that a definite association exists The phenomenal increase in lung cancer mortality and
widespread
have been
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in tobacco as a possible etiological agent
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that, when unbiased histories were obtained from cancer *patients* and *proper controls*, probably no association between smoking and cancer would appear However, our analysis of the records of 3659 cancer patients and 1348 patients with other diseases showed a significantly higher proportion of cigarette smokers among patients with two forms of cancer, that of the lung and the larynx There was found also a significant association between pipe smoking and lip cancer

The figures for lung and larynx cancer are presented in *Table 4* From these data the indicated incidence among cigarette smokers

TABLE IV

Cigarette Smokers among Male Patients (1) — 1938 50
Lung Cancer, Larynx Cancer, Diseases other than Cancer

Age	Number Persons			Cigarette Smokers Per cent			Ratio of r = Lung Cancer Incidence (2) Smokers / Non Smokers	
	Lung Cancer	Larynx Cancer	Non Cancer	Lung a1	Larynx a2	Non Cancer b	Lung Ca	Larynx Ca
Under 55	103	71	670	87 6	84 5	65 0	4 0	3 1
55 64	130	94	345	79 2	76 0	49 6	[illegible]9	3 3
65 and over	65	80	333	[illegible] 8	78 8	23 4	3 8	2 1
Total	00	245	1348	76 7	66 5	50 3		

(1) At Roswell Park Memorial Institute, Buffalo, N Y

(2) Calculated from the formula $\text{Ratio} = \frac{a - ab}{b - ab}$, where a and b are, respectively, the proportion of smokers in the cancer and control populations This procedure assumes that the cancer groups are representative, as to smoking of all such cases and the control group is representative of the general population not having cancer The use of the formula is equivalent to distributing the total population, with respect to smoking in the same way as the control group and the cancer population in the same way as the cancer group and then calculating the age specific rates This formula and this procedure is slightly inaccurate in that the proper distribution of smokers in the total population should include the smokers in the cancer population However, since the latter is small compared to the total population, the error thereby introduced is insignificant This error can be eliminated by substituting for (b), b + L (a — b) where L = incidence of lung cancer in the general population

TABLE V

Lung Cancer and Smoking Indicated Incidence and Proportion Attributable to Smoking in Four Studies

Authors	Per Cent Cigarette Smokers among		Ratio of Incidence		Indicated per cent of all lung cancer « attributable to smoking »
	Lung Cancer Cases (a)	Controls (b)	Smokers / Gen. Pop $i = \frac{(a)}{(b)}$	Smokers / Non Smokers $r = \frac{a - ab}{b - ab}$	$S = \frac{b(r-1)}{b(r-1)+1}$
1) Doll & Hill (5)	99 7	96 0	1 04	13 8	92 5
2) Wynder & Graham (11)	98 7	85 4	1 16	12 9	91 0
3) Breslow (2)	91 0	69 5	1 31	4 4	70 3
4) Levin et al (1)	78 2	49 9	1.57	3 6	56 5
5) Levin et al (2) adjusted to (3)	91 0	58 1	1 57	7 3	78.5
6) Doll & Hill (3) excluding 1 4 cigarette smokers	96 0	90 5	1 07	2 8	61 7

(1) Adjusted to age distribution of data of (1) Doll and Hill

(2) By bringing percentage of smokers in lung cancer cases to same percentage as in (3) and increasing percentage in controls proportionately

(3) From Table VI Doll and Hill (5)

is approximately four times as much for lung cancer and three times as much for larynx cancer, as in non-smokers

The studies of DOLL and HILL and of WYNDER and GRAHAM would indicate a much greater excess incidence among smokers as compared with non smokers The comparative figures in *Table 5* are presented chiefly to point out the different conclusions as to relative magnitude of the possible effect of smoking which may be reached from different types of data Three measures of the association of smoking with lung cancer are tabulated in the last three columns of *Table 5*

The first, $i = \frac{a}{b}$, gives the ratio of incidence among smokers compared to that in the general of total population In *Table 5*, this index, which depends in magnitude on the difference between a and b, is smallest in the DOLL and HILL data, and largest in ours This index is not a good measure of the comparative effect of smoking If almost all persons smoked, (i) would be close to 1 0, but this would be compatible with a high excess incidence among smokers

The second index, (r), is the ratio of lung cancer incidence among smokers to that among non-smokers It seems paradoxical that this index shows inverse relative magnitude, in *Table 5*, to the values for (i) This is because the magnitude of (r) is dependent chiefly on how close (a) approaches to unity The closer (a) comes to 1, the closer b — ab comes to 0 (if a = 1, b — ab = 0) and the closer any value divided by b — ab comes to infinity In *Table 5*, the smallest difference as to smoking between the lung cancer and the control group is found in line (1), but this would also indicate the greatest excess incidence among smokers and the smallest incidence among non smokers, because (a) is very close to 1 (997) This may seem to be largely a statistical peculiarity, serving to throw doubt on the validity of the formula used to calculate (r) This formula however is only another way of distributing the lung cancer population and the general population in the same way, as to smoking, as the lung cancer and control groups of the studies are distributed, and then calculating comparative lung cancer rates among smokers and non-smokers When (a) approaches 1 00, the formula is merely a numerical way of saying « if all or nearly all lung cancer cases smoke, then lung cancer occurs solely or almost solely among smokers », or « lung cancer never, or very rarely, occurs among non-smokers » If lung cancer occurred only among smokers, this would be compatible with the conclusion that smoking was an essential cause of lung cancer Since lung cancer is known to occur in non smokers, smoking cannot be an esssential cause of the disease

One of the points to be made, from this analysis, is that in studies of the association of s [illegible] moking [illegible] of the [illegible] by relatively small differences between the control and test groups, when the general prevalence of the environmental factor is high Thus, in *Table 5* if the percentage of smokers in the lung cancer group in line (1) were 98 7 instead of 99 7, the indicated fi [illegible]

ked more than 1-4 cigarettes were excluded from the category of smokers, the figures for line (1) would be those in line (6), and (r) would be only 2 8

The third index in *Table 5*, (S) is the indicated maximum proportion of lung cancer attributable to smoking (4) This index is based on the assumption that smokers, if they had not become smokers, would have had the same incidence of lung cancer as that found among non smokers This assumes that other etiological factors are equal in the two groups

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(4) The formula for this index $S = \frac{b(r-1)}{b(r-1)+1}$, is derived as follows:

Where X = incidence of lung cancer in non smokers
rX = incidence of lung cancer in smokers
b = proportion of general population classified as smokers
$1-b$ = proportion of general population classified as non smokers
$rXb + X(1-b)$ = incidence of lung cancer in total population
$\frac{r-1}{r}$ = proportion of lung cancer in smokers attributable to smoking

$$S = \frac{\frac{rXb\ r-1}{r}}{rXb+X(1-b)} = \frac{\frac{rb\ r-1}{r}}{rb+(1-b)} = \frac{b(r-1)}{b(r-1)+1}$$

give up smoking have less lung cancer as a result, this would be confirmatory evidence of the causative effect of smoking The studies already reported may be considered as studies of the preventive effect of not smoking, if we can assume that smokers do not differ significantly from non smokers with respect to other possible causative factors « Prospective » studies of persons who do not smoke would not be essentially different, as to scientific validity, from those already reported using the history or « retrospective » method The data of DOLL and HILL showing a definite increase in lung cancer with amount of smoking may be considered as a further example of the test of prevention, since it may be considered an indication of the effectiveness of *reduction* in smoking A further test could be made if a representative sample of smokers could be persuaded to stop smoking and their subsequent lung cancer incidence compared with their fellows One of the difficulties in such a study would be to be certain that those who stopped smoking were comparable in all other respects to those who did not Identification and elimination of the agent in tobacco which is responsible for the carcinogenic effect would make possible a further definitive test of prevention

The evidence with respect to tobacco and lung cancer does not rule out the possibility that the carcinogenic effect of smoking may be wholly or partly dependent on the co existence of other factors, which, if eliminated or reduced, would correspondingly eliminate or reduce the smoking effect Such factors

ceptibility plays a major role is strongly suggested by the fact that a large proportion of

r

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between these who do and do not develop lung cancer after exposure to the same amount of smoking or other known or suspected etiological factors

What is known of the occurrence of lung cancer in man is consistent with the conclusion that tobacco is one of the major factors in the causation of cancer at present It does not seem to be the only important factor Other etiological factors may be responsible for 25 to 50 per cent of the cases in males

DISCUSSION

DR KORTEWEG Mr Chairman, I should like to warn against using the method of Cornfield automatically as is being done in several papers of the last years The formula is

$$A = \frac{p1\ (1 - p2)}{p2\ (1 - p1)}$$

A being the relative amount by which the disease — that is lung cancer — is augmented by the possession of the attribute, in this case smoking

p1 = the proportion of smokers among those with cancer of the lung

p2 = the proportion of smokers among those without cancer of the lung

In this formula (1 — p1) is the dangerous point In Doll and Hill s investigation according to this formula A = 14 and (1 — p1) = 0,003 This factor, 0 003 results from the fact that in 649 lung cancer patients there were found two non smokers only This figure of two was mere chance Just as well it could have been three or one or even four or 0 However, if it were four the augmentation factor would have changed from 14 in 7, if no non smokers had been found, this factor would have changed in infinitely

In lung cancer patients the percentage of non smokers is always low The better and the more thorough the investigation, the lower the percentage which will be found One moment of inattention from the side of the almoner may cause a noteworthy increase to the percentage

Certainly Cornfield lays stress on the fact that in his procedure the assumption is made that the diseased and the control groups are representative of the same groups in the general population If this assumption is not satisfied then neither the rates the relative frequencies nor any other statistics calculated from the data will have applicability beyond the particular group studied

In my opinion the vagueness of the definition whom we should consider a non smoker, makes exact computations impossible We, therefore should better confine ourselves to the statement that according to Doll and Hill and to all other investigators a strong positive correlation between heavy smoking and lung cancer exists

DR DOLL Our later series of 1357 cases gives an augmentation figure of 8 (c f 14

in previous series) This is based on 7 non smokers and bears out Dr Korteweg s argument

DR HAMMOND The difficulty lies not in the formula but in the method of experimentation We are trying to draw conclusions with regard to whole populations from data obtained from relatively small samples

DR DORN The point mentioned by Dr Korteweg is partially taken care of by the computation of the standard error of the ratio As this ratio becomes unreliable the size of the standard error increases, indicating that ratio may vary over a large range and that we have a rather imprecise estimate of the true value

DR DOLL I would add another word of caution about this sort of comparison between different countries Twenty cigarettes a day is not necessarily the same thing in all countries Apart from the variation in the

DR STEWART There is also the question of whether the first or the last part of the cigarette is most harmful

DR LEVIN The method of estimating the standard error in this case is different It was assumed that these comparisons were only valid if the standard error was outside the range of chance If we had 12 000 cases instead of 1200 the standard error would be decreased

ariables e whole impor isely as possible

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ZUSAMMENFASSUNG

Bevolkerung Es wird die Meinung vertreten, dass Umweltsfaktoren fur das vermehrte Auftreten des Lungenkarzinoms verantwortlich *gemacht werden mussen wenn diese Zunahme eine wirkliche ist. Es* werden die Unterschiede aufgezeigt fur die Haufigkeit dieser Krankheit je nach Geschlecht und Alter

Eine wirkliche Zunahme des Lungenkarzinoms kann nicht ausgeschlossen werden und diese Zunahme scheint am besten den gefundenen Tatsachen zu entsprechen Das Maximum in der Alterskurve wird auf Grund einer strengen Beurteilung der Tatsachen erklart Danach wird fur die nächsten zehn Jahre fur New York eine bedeutende Zunahme der Lungenkarzinome vorausgesagt Die Verff diskutieren die verschiedenen Untersuchungen uber die Beziehung zwischen Rauchen und Lungenkarzinom. Daraus lasst sich ableiten dass bei den Zigarettenrauchern das

Lungenkarzinom 4 bis 7 mal haufiger auftritt, als bei Nichtrauchern und dass 50 bis 75 % der Lungenkarzinome bei Mannern auf das Rauchen zuruckgefuhrt werden konnen Es werden die Zusammenhange zwischen gleichzeitigem Vorkommen der Krankheit und Verursachung derselben diskutiert und es wird besonders *hervorgehoben*, dass « kausaler Faktor » nicht « alleiniger kausaler Faktor » bedeuten muss Schliesslich werden praktische Methoden in Erwagung gezogen um kausale Teste zu finden im Hinblick auf das Rauchen als mogliche Ursache.

SUMMARY

The terms Endemiology and Epidemiology are being discussed, and a new general term Demiology proposed to indicate the synthesis of knowledge regarding the « normal » occurrence of a disease in the general population and its higher (or lower) than normal occurrence in sub groups *of that population* It is supported that there must be looked for some environmental factors if the increase in lung cancer incidence is real Sex and age differences in the recorded increase in lung cancer mortality are shown, and it is stated that a real increase in incidence can

dated on the basis of a cohort analysis, and it has been found that even a conservative projection of the cohortal rates for New York State predicts a marked increase in lung cancer within the next decade Various investigations on lung cancer and smoking are being discussed, and three measures of the association of smoking and lung cancer are computed for different materials On the basis of these studies it is concluded that lung cancer incidence among cigarette smokers is 4 *to 7 times as high as among non* smokers, and that 50 to 75 per cent of lung cancer in males is attributable to smoking The relation between association and causation is further discussed, and it is stressed that « causative factor » not means « sole causative factor » Finally practical ways in testing causation are considered in the light of smoking as a *possible cause*

RESUMEN

Se discuten los terminos endemiología y epidemiologia y se propone un nuevo termino « Demiologia » para indicar la sintesis de conocimientos en lo que se refiere a la frecuencia « normal » de una enfermedad en la población general y su frecuencia mayor o menor de lo normal en subgrupos de dicha población Se insiste en que deben bucarse algunos factores am*bientales para explicar* la mayor frecuencia del cáncer pulmonar Se exponen las diferencias de sexo y edad en el aumento registrado de la mortalidad por cáncer de pulmón y se afirma que no puede excluirse un aumento efectivo de la frecuencia *y que este au*mento parece ser la explicación mas razonable de los hechos observados El vértice de la curva de mortalidad específica en cuanto a la edad se explican mediante *análisis de cohortación y* se ha observado que incluso una interpretación prudente de las cifras de cohortación del estado de Nueva York predice un aumento notable del cáncer de pulmon en los próximos diez años Se analizan varias investigaciones sobre el cáncer pulmonar y el abuso del tabaco y se somputan tres medidas de la asociación tabaco cáncer pulmonar en *relación con diferentes materiales Basándose en estos estudios se llega a la conclusión de que la fre*cuencia de cáncer pulmonar en los fumadores de cigarrillos es de 4 a 7 veces mayor que en los no fumadores y de que del 50 al 75 por ciento de los cánceres pulmonares en el varón es atribuíble al tabaco Se comenta luego la relación entre asociación y causalidad y se insiste en que *« factor causal » no quiere decir* « único factor causal » Por último se consideran algunos *procedimientos prácticos de comprobar la cau*salidad en relación con el tabaco como posible causa

RESUME

Les termes endémiologie et épidémiologie ont été discuté et un nouveau terme général a été propose pour désigner l'ensemble de nos connaissances se rapportant d'une *part* à la distribution normale d'une maladie dans une population donnée, d'autre part, à la distribution plus ou moins grande par rapport à la normale dans certains sous groupes de cette même population

On a maintenu l'idée qu'il fallait rechercher les influences du milieu environnant pour expliquer *l'augmentation d'incidence* des cancers du poumon si celle ci est réelle

Les A font ressortir les differences de fréquence liées aux différences de sexe et aux differences d'âge, ils établissent qu'on ne peut exclure une réelle augmentation des cancers du poumon A leur avis, cet accroissement semble être la meilleure explication des *faits observés Le sommet de la courbe donnant l'incidence en fonction de* l'âge est expliqué en se basant sur une analyse serrée des faits Ces analyses font prévoir pour New York City, une augmentation d'incidence des cancers du poumon *au cours de la pro*chaine décade

Les Auteurs discutent differentes études statistiques se réferant aux relations qui existent entre *le fait de* fumer et le cancer du poumon Il ressort de ces faits, que l'incidence du cancer du poumon est de 4 à 7 fois plus elevée chez les fumeurs de cigarettes que chez les *non fumeurs et que chez les hommes*, 50 à 75 % des cancers du poumon doivent être attribués au fait de fumer Les Auteurs discutent ensuite les concepts « associations » et « causes » et ils insistent sur *le fait* que le « facteur causal » ne signifie *pas necessaire*ment « seul facteur causal »

Finalement des methodes pratiques de test causal sont envisagées et ce, a la lumiere du fait que l'habitude de fumer est une cause possible

RIASSUNTO

I termini « endemiologia » ed « epidemiologia » vengono discussi ed un nuovo termine generale è stato proposto per definire l'insieme delle nostre conoscenze che riguardano da una parte la distribuzione normale di una malattia in una determinata popolazione e dall'altra la distribuzione variabile in confronto alla norma in questa stessa popolazione. È stato sostenuto che si dovevano prendere in considerazione particolari fattori ambientali per spiegare se l'aumento di frequenza del cancro del polmone è sicuro.

Gli AA. sottolineano la differente frequenza legata al sesso ed all'età e affermano che non si può esclu

[illegible]

riscono ai rapporti tra fumo e cancro del polmone. In base a tali lavori si conclude che la frequenza del cancro del polmone nei fumatori di sigarette è di 4 7 volte più elevata in confronto ai non fumatori, e che nel sesso maschile il cancro del polmone deve essere

[illegible]

mente « unico fattore causale ».

Infine sono valutati i metodi pratici per definire i fattori causali ed a questo riguardo l'abitudine di fumare è considerata una possibile causa.

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés.

Nous le regrettons et nous en excusons vivement.

La Rédaction

CANCER OF THE LUNG IN VIENNA

BY

J KRETZ

(Oesterreichische Gesellschaft fur Erforschung und Bekampfung der Krebskrankheit Wien)

The extension of the average life span which has taken place during the last decades is thought to be a main cause of the increase of mortality from cancer observed in all civilized countries By comparison of official census in Austria from the years 1910 and 1934 with a census for the year 1951 we can estimate to which extent a change in the distribution by age of the population has influenced the increase of fatal cases of cancer and above all the increase of cancer of the lung

The official censusses for the years 1910 1934 and 1951 give the structure of the population according to sex and age class and since there are comparatively long periods of observation between these censusses eventual changes can be established beyond doubt

Table 1 gives the distribution by age for each sex of the total population Because of the subordinate importance of the age classes 0 29 years these are represented by a single group

Table 2 represents the number of fatal cases of cancer for the years 1910 1934 and 1951 The official cancer mortality statistics in Vienna are ordinarily based on the death certificates furnished by the district physician In cases of doubt about the true cause the district physician asks for a postmortem examination by the sanitary police. The cancer diagnosis and the official mortality statistics in Vienna are very reliable because according to earlier examination the cancer diagnosis of about two thirds of persons dying from cancer were confirmed in hospitals Camouflaged diagnoses as emaciation *senility etc have not been used in official* statistics for more than 20 years

It would be erroneous to give the absolute number of deaths in proportion to the total population because as evident from *table 1* the older part of the latter has increased considerably For this reason the mortality rate for cancer should be computed for the population of the same age group at any particular time

It appears from *table 3* and the corresponding graph in *fig 1* that for both sexes the increase in the rate of cancer mortality with age may be represented by a curve of almost parabolic shape A comparison of the curves

TABLE I

Population distributed according to sex and age in groups of one thousand (1910 Persons present 1934 and 1951 Permanent residents)

Year	Sex	Classes of age						
		0 29	30-39	40 49	50 59	60 64	over 65	Total
1910	Males	550 [illegible]	169 0	116 [illegible]	77 6	[illegible]5 [illegible]	34 7	973 6
	Females	569 6	180 0	1[illegible] 7	4 1	33 3	55 1	10[illegible]7 8
1934	Males	334,5	159 8	133 6	117 0	41 3	60 [illegible]	846 4
	Females	364 6	194 6	173,5	146 6	[illegible]3 8	94 6	10[illegible]7 7
1951	Males	[illegible]86 6	85 8	145 4	1[illegible]	46 4	8[illegible] 5	773 6
	Females	[illegible]96 0	1[illegible] 8	183 6	168 0	73 7	143 [illegible]	987 [illegible]

TABLE II

Deaths from Cancer and other Malignant Tumours in Years of Census 1910 1934 and 1951

Year	Classes of Age													Total
	0-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	over 85	
ABSOLUTE FIGURES														
MALES														
1910	37	20	35	6[illegible]	9[illegible]	143	18	196	177	118	5[illegible]	23	11	1 159(1)
1934	21	12	20	42	89	184	[illegible]7	304	34[illegible]	306	148	68	14	1 82[illegible]
1951	1[illegible]	2	15	47	100	[illegible]06	317	408	4[illegible]6	455	345	149	4[illegible]	2 579
FEMALES														
1910	3	26	6[illegible]	89	132	180	198	212	194	143	88	3[illegible]	7	1 399(2)
1934	18	34	56	95	154	205	[illegible]54	[illegible]71	296	29[illegible]	2[illegible]5	111	40	2 041
1951	5	17	46	78	167	216	68	345	395	454	390	210	83	[illegible] 694
BOTH SEXES														
1910	69	46	100	156	[illegible]4	3[illegible]3	380	408	[illegible]71	261	144	55	18	[illegible] 558(3)
1934	39	46	76	137	243	389	5[illegible]6	5[illegible]5	638	588	373	1[illegible]9	54	3 863
1951	42	19	61	1[illegible]5	267	4[illegible]	595	753	871	909	735	359	1[illegible]5	5 273
PER 100 000 LIVING OF SAME AGE														
MALES														
1910	6 7	[illegible]3 3	44,2	105 4	172 5	3[illegible]6 [illegible]	537 8	779 1	1025 6	11[illegible]5 8	117[illegible] 8	1161 6	1617 6	119 0
1934	6 3	14 [illegible]	26,5	6[illegible] 5	133 8	299 0	4[illegible] 5	734 5	1[illegible]03 6	1734 [illegible]	1675,2	1984 2	1543 5	215 3
1951	6 0	5 1	[illegible]9 6	71 1	135 8	300 1	5[illegible]0 7	850 7	1[illegible]73 1	1711 4	2306 0	2656 4	2550 1	335 2
FEMALES														
1910	5 6	[illegible]6 9	77 9	131 [illegible]	2[illegible]8,3	348 7	466,5	636 5	77[illegible] 9	864 8	1046 6	841,2	489 9	13[illegible],3
1934	4 9	34 6	58 1	107 2	181 0	[illegible]68 0	360 9	502 7	[illegible]41 7	10[illegible]6 6	1401 9	1513,9	1634 7	198 6
1951	8 4	32 0	65 5	87 0	177 9	240 5	3[illegible]9 8	495 6	658 5	1003 0	1385 0	1[illegible]85 6	19[illegible]9 4	270,3
BOTH SEXES														
1910	6[illegible]	[illegible]4 7	61,5	118 7	[illegible]01,5	338 4	498 1	697,9	87[illegible] [illegible]	98[illegible] 1	103[illegible],3	950 9	853 5	125 9
1934	5 6	[illegible]	44 2	87,3	160 3	[illegible]81 8	41[illegible] 6	603 4	933 8	1303 4	1498 9	1663 7	1610 0	206 1
1951	[illegible]	[illegible]0 6	50 4	80[illegible]	159 4	[illegible]66 4	4[illegible]7 6	635 4	894,5	1[illegible]65 [illegible]	1[illegible]04 6	[illegible]006 8	21[illegible]4 8	298 6

(1) Including [illegible] persons of unknown age
(2) Including 1 person of unknown age
(3) Including 3 persons of unknown age

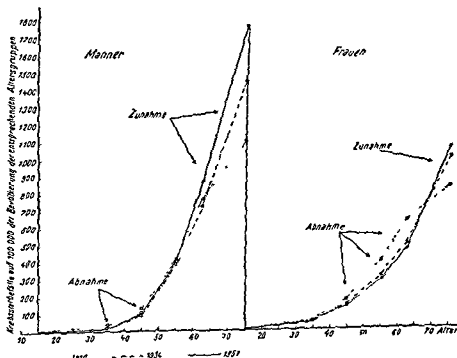
for the years 1910 1934 and 1951 shows a small decrease of cancer mortality for men of the age classes 30 59 years and a much more pronounced decrease for women between the ages 30 and 64 Besides it follows that the great increase of cancer mortality for men begins after the 60th and for women after the 55th year of life This increase noticeably surpasses the decrease in cancer mortality for the younger age classes so that as a whole the result is an increase of cancer mortality during the last decades

TABLE III.

Deaths from Cancer of Respiratory System, Cancer of all Sites, and total of death in Wien (¹) from 1931.

Year	All deaths	Cancer all sites			Cancer of respiratory system					
					Men		Women		Persons	
		Men	Women	Persons	Abs	% of all sites	Abs.	% of all sites	Abs	% of all sites
1931	24 363	1 639	1 975	3.614	259	15,80	54	2,73	313	8,66
1932	23 405	1 653	1 900	3 553	260	15,73	65	3,42	325	9,15
1933	23 471	1 727	2 051	3 778	284	16,44	71	3,46	355	9,40
1934	22 577	1 822	2 041	3 863	302	16,58	61	2,99	363	9,40
1935	24 253	1 864	2 021	3 885	322	17,27	50	2,47	372	9,58
1936	23 669	1.993	2 285	4 278	367	18,41	85	3,72	452	10,57
1937	24 453	1 989	2 198	4 187	397	19,96	93	4,23	490	11,70
1938	25 932	2 042	2 227	4.269	422	20,67	87	3,91	509	11,92
1939	31 133	2 141	2 251	4 392	485	22,65	119	5,29	604	13,75
1940	31 222	2.286	2 486	4 772	472	20,65	98	3 94	570	11,94
1941	28 811	2 241	2 547	4 788	461	20,57	85	3,34	546	11,40
1942	29 510	2 272	2 466	4 738	483	21,26	98	3 97	581	12,26
1943	29 176	2 120	2 363	4 483	489	23,07	85	3,60	574	12,80
1944	35 151 (²)	2 074	2 449	4 523	445	21,46	116	4,74	561	12,40
1945	62 335 (³)	1 942	2 315	4 257	400	20,60	88	3,80	488	11,46
1946	28 329	1 843	2 123	3 966	483	26,21	91	4,28	574	14,47
1947	25 279	2 105	2 247	4 352	581	27,60	100	4,45	681	15,65
1948	23 088	2 081	2 414	4 495	617	29,65	112	4,64	729	16,22
1949	24 304	2 278	2 529	4 807	695	30,51	126	4,98	821	17,08
1950	24 249	2 467	2 572	5 039	753	30,52	123	4,78	876	17,38
1951	25 872	2.579	2 694	5 273	819	31,76	125	4,64	944	17,90

(1) Wien up to 1938 21 districts, from 1939 26 districts
(2) Comprising 3 998 civilians killed by actions of war
(3) Comprising 7 016 civilians killed by actions of war



However a statistical examination was necessary in order to see whether the changes of the relative frequency of cancer was statistically significant

Thus the values of χ^2 was calculated according to the usual biostatistical methods and the following results were obtained for the years 1935 and 1951 for men and women separately

It is evident from a comparison of cancer mortality in the different age classes that there is a significant increase in the values

TABLE IV

Mortality from Cancer

(Deaths from cancer per 100 000 inhabitants of corresponding age classes)

Year	Sex	Classes of age						
		0 29	30 39	40-49	50-59	60-64	over 65	Total
1910	Males	7	33	136	419	[illegible]	1110	119
	Females	6	51	1 6	40[illegible]	63	84	13[illegible]
1934	Males	6	0	98	390	73[illegible]	1459	1[illegible]
	Females	5	46	144	313	504	1009	199
1951	Males	6	[illegible]0	101	413	8 0	1 77	333
	Females	8	51	133	[illegible]89	469	1070	[illegible]73

TABLE V

WIEN — MALES

Mortality from cancer according to site for the years of 1934 (top) 1951 (bottom) and value of χ (right)

(Given as rate per 100 000 inhabitants of corresponding age classes)

Increase: **heavy type** Decrease: *Italics*

Site	Classes of age											
	0-29		30-39		40-49		50-59		60-64		over 65	
Mouth and pharynx	0,3 0 0	0 9	0 0 0 0	0 0	6 0 1 4	*4,2*	[illegible]8[illegible] 8 7	*13 1*	38 7 30,2	0 5	54 8 43 6	0 [illegible]
Respiratory system	0 3 0 0	0 9	1 9 [illegible],3	0 1	[illegible]1 0 37 1	**6 1**	88 9 186,9	**41 1**	164 6 34[illegible] 7	**26 6**	16[illegible] [illegible] 444 9	**84 8**
Oesophagus and stomach	0 3 0 3	0 0	6 9 9 3	0 6	3 [illegible] 9 18 6	*5 6*	136 8 76 5	*21 1*	[illegible]17,9 183,2	1,3	508,3 437 6	*4,0*
Intestine	0 3 0,3	0 0	3 1 1 [illegible]	0 8	1[illegible] 7 13 1	0 1	47 9 37 1	1 8	140 4 81 9	*6,8*	330 6 276 4	1 9
Liver biliary passages pancreas	0 0 0 3	0 9	1 9 0 0	1 8	14 [illegible] 1[illegible] 4	0 1	38,5 37 1	0,3	75 1 109 9	[illegible] 8	144,5 181 8	[illegible] 8
Genitourinary system	1 [illegible] 0 3	1 4	3 1 [illegible] 3	0 1	4,5 [illegible] 8	0 6	[illegible]6 5 25 [illegible]	0,2	60 5 60,3	0 0	[illegible]07 6 23[illegible] 4	7 6

TABLE VI

WIEN — FEMALES

Mortality from cancer according to site for the years of 1934 (top), 1951 (bottom), and value of χ^2 (right).

(Given as rate per 100,000 inhabitants of corresponding age classes)

Increase . heavy type. Decrease . *italics*

Site	Classes of age											
	0-29		30-39		40-49		50 59		60-64		over 65	
Breast	0,8 0,7	0,0	4,6 11,4	5,1	25,0 24,5	1,4	51,8 42,9	1,7	40,9 48,8	0,4	93,0 120,8	3,9
Respiratory system	0,0 0,3	1,0	3,1 3,3	0,1	4,6 6,0	0,5	7,5 13,7	2,8	14,9 28,5	2,7	29,6 45,4	3,9
Oesophagus and *stomach*	0,8 *1,4*	0,1	5,7 *4,0*	0,2	12,1 *14,7*	0,7	46 4 35,7	2,3	132,0 73,3	*11 0*	318 0 269,6	*4,5*
Intestine	0,5 0,3	0,1	3,6 3,3	0,1	11,5 7,6	1,5	38,2 30,4	1,5	63,2 61,1	0,1	167,0 168,3	0,4
Liver, biliary passages, pancreas	0,3 0,3	0,0	1,5 0,0	2,1	9,2 6,5	1,0	41,6 31,0	2,7	83,6 67,8	1,0	148,0 176,7	2,7
Genito urinary system	*0,8* *2,0*	1,1	24 2 22,0	0,3	71,5 61,0	1,5	*105,0* *104,6*	0,2	132,0 145,2	0,3	158,6 200,4	5,2

for carcinoma of the respiratory organs from the age of 40 and onwards In this group cancer of the lung covers about 95 per cent and thus the statistics prove that the increase in cancer of the lung in Vienna does not only counterbalance the decline in mortality from cancer of other sites, but also that it is the main reason of the constant increase in the mortality from cancer in the population of Vienna

For women the increase in cancer of the lung is only evident after the 65th year of age, and even there not to any considerable extent

Austrian Cancer Society Among the three

ches of industry (17 2 %).

People occupied in farming and forestry show the highest cancer frequency for the skin, the clothing industry for the rectum, and commerce for the stomach Among people occupied in public administration, and people unoccupied, cancer of the prostate takes the first place

DISCUSSION

DR STEINER : Dr. Kretz mentioned the possible role of influenza I experimented with two strains of mice One had a high frequency of spontaneous lung tumour — 70 per cent — at an age of 18 months and the other strain had a negligible frequency of under two per cent at an age of 24 months I exposed them in a chamber to influenza type A virus (strain PR8) and followed them throughout their life span except for certain individuals which were studied early for adequacy of exposure I will now show slides (Ref. *Cancer Research*, 10 ; 385, June, 1950)

The first slide shows a drawing of a hu-

TABLE VII

Deaths from cancer and other malignant tumours according to site

MALE DEATHS

ABSOLUTE FIGURES

Year	0-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	over 85	Total
	Classes of Age													
Mouth and Pharynx (1934 and 1951 Nr 45)														
1934	1	—	—	3	5	11	20	16	15	8	3	7	—	91
1951	—	—	—	1	1	6	5	14	10	13	10	3	—	63
Intestinal Canal and Peritoneum (1934 and 1951 Nr 46)														
1934	2	4	15	27	51	108	153	179	233	205	109	36	10	1 134
1951	3	1	8	17	47	74	124	174	228	216	193	82	25	1 102
Respiratory System (1934 and 1951 Nr 47)														
1934	1	1	2	7	21	41	63	68	52	32	12	2	—	302
1951	—	1	1	17	37	91	146	159	157	119	68	21	2	819
Mammary Gland (1934 and 1951 Nr. 50)														
1934	—	—	—	—	—	—	1	—	—	—	—	—	—	1
1951	—	—	—	—	1	—	1	1	1	1	2	—	—	7
Other Sites (1934 Nr 51-53 and 1951 Nr 51 55)														
4	17	7	3	5	10	22	35	41	42	61	24	23	4	294
4 51	14	—	6	12	14	35	41	60	80	106	72	43	15	498

PER 100,000 LIVING OF CORRESPONDING AGE CLASSES

Year	0-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	over 85	Total
	Classes of Age													
Mouth and Pharynx (1934 and 1951 Nr 45)														
1934	0,3	—	—	4,5	7,5	21,1	36,0	38,7	52,8	45,3	34,0	204,2	—	10,8
1951	—	—	—	1,5	1,4	8,7	9,0	29,5	26,7	48,9	66,8	53,5	—	8,2
Intestinal Canal and Peritoneum (1934 and 1951 Nr 46)														
1934	0,6	4,7	19,9	40,2	79,7	175,5	275,3	432 5	820,0	1161,9	1233,7	1050,5	1102,5	134,0
1951	1,0	2,5	15,8	25,7	63,8	107,8	223,2	366,7	609,8	813 4	1290,0	1461,9	1517,9	154,9
Respiratory System (1934 and 1951 Nr 47)														
1934	0,3	1,2	2,6	10,4	31,6	66,6	113,4	164,3	183,0	181,4	135,8	58,4	—	33,7
1951	—	2,6	2,0	25,7	50,2	132,8	292,9	335,0	419,9	447,6	454,5	374,4	121,4	106,5
Mammary Gland (1934 and 1951 Nr. 50)														
1934	—	—	—	—	—	—	1,8	—	—	—	—	—	—	0,1
1951	—	—	—	—	1,4	—	1,8	2,1	2,7	3,8	13,4	—	—	0,9
Other Sites (1934 Nr 51-53 and 1951 Nr 51 55)														
1934	5,1	8,3	4,0	7,4	13,0	35,9	63 0	99,0	147,8	345,7	271,7	571,1	441,0	34,7
1951	5,0	—	11,8	18,2	19,0	51,0	73,8	126,4	214,0	308,7	481,3	766,8	910,9	64,7

Numbers indicate site according to the International System,
for 1934 the system of 1929,
& for 1951 the system of 1938

TABLE VIII.

Deaths from cancer and other malignant tumours according to site

FEMALE DEATHS

ABSOLUTE FIGURES

Year	0-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	over 85	Total
	Classes of Age													
Mouth and Pharynx (1934 and 1951 Nr 45)														
1934	—	—	—	—	2	1	—	—	4	—	—	2	—	9
1951	1	—	1	—	2	—	3	2	3	2	5	2	—	21
Intestinal Canal and Peritoneum (1934 and 1951 Nr 46)														
1934	6	9	12	24	33	63	122	150	174	176	155	78	26	1 028
1951	7	4	6	18	37	62	105	151	209	259	235	131	53	1 276
Respiratory System (1934 and 1951 Nr 47)														
1934	—	4	2	6	2	6	5	8	9	9	5	4	1	61
1951	1	1	3	4	7	17	6	21	11	24	18	10	2	125
Female Genital System (1934 and 1951 Nr 48 and 49)														
1934	3	17	30	41	83	87	67	71	50	55	31	11	3	549
1951	6	6	20	30	78	86	80	102	93	72	46	24	12	655
Mammary Gland (1934 and 1951 Nr. 50)														
1934	3	1	8	18	27	32	44	22	26	28	21	9	4	243
1951	2	2	12	16	29	31	41	36	47	52	38	23	13	342
Other Sites (1934 Nr 51 53 and 1951 Nr 51 55)														
1934	6	3	4	6	7	16	16	20	33	14	13	7	6	151
1951	8	4	4	10	14	20	33	33	33	45	48	20	3	275

PER 100,000 LIVING OF CORRESPONDING AGE CLASSES

Year	0-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	over 85	Total
	Classes of Age													
Mouth and Pharynx (1934 and 1951 Nr 45)														
1934	—	—	—	—	2,4	1,3	—	—	10,0	—	—	27,3	—	0,9
1951	0,3	—	1,4	—	2,1	—	3,7	2,8	5,0	4,4	17,8	17,0	—	2,1
Intestinal Canal and Peritoneum (1934 and 1951 Nr 46)														
1934	1,7	9,2	12,4	27,1	38,8	82,4	173,3	278,[illegible]	436,0	640,7	965,7	1063,8	1062,5	100,0
1951	2,4	7,5	8,5	20,1	39,4	69,0	129,2	212,5	346,8	572,2	834,6	1113,9	1251,2	128,0
Respiratory System (1934 and 1951 Nr 47)														
1934	—	4,1	2,1	6,8	2,4	7,8	7,1	14,8	22,5	32,8	31,2	54,6	40,9	5,9
1951	0,3	1,9	4,3	4,4	7,5	18,9	7,4	20,6	18,3	53,0	63,0	85,0	47,2	12,6
Female Genital System (1934 and 1951 Nr 48 and 49)														
1934	0,8	17,3	31,1	46,2	97,5	113,8	95,2	131,7	125,3	200,2	193,2	150,0	122,6	53,4
1951	2,0	11,3	28,5	33,5	83,1	95,8	98,5	143,6	155,0	159,1	163,4	204,1	283,2	65,7
Mammary Gland (1934 and 1951 Nr. 50)														
1934	0,8	1,0	8,3	20,3	31,7	41,8	62,5	40,8	65,2	101,9	130,8	122,7	163,5	23,7
1951	0,7	3,8	17,1	17,8	20,9	34,5	50,4	50,7	78,4	114,9	134,9	195,6	306,9	34,3
Other Sites (1934 Nr 51 53 and 1951 Nr 51 55)														
1934	1,6	3,0	4,2	6,8	8,2	20,9	22,8	37,1	82,7	51,0	81,0	95,5	245,2	14,7
1951	2,7	7,5	5,7	11,2	14,9	22,3	40,6	46,4	55,0	99,4	170,4	170,0	70,8	27,6

Numbers indicate site according to the International System,
for 1934 the system of 1929,
and for 1951 the system of 1938

man lung based on the influenza epidemic of 1918 to 1919 In the recovery stage there was a tremendous overproduction of epithelial tissue On the basis of this type of evidence it was predicted that we could expect an increase in human lung cancer in subsequent years When that increase materialized this influenzal etiology theory gained credence In mice we produced the same lesion but it never went on to a tumour Second slide shows the microscopic section of a mouse lung after exposure to influenza virus Third slide shows an epithelial overgrowth which looks like pre-cancer Fourth slide shows lung with area of older influenzal lesions The influenza virus although it is a powerful epithelial cell stimulus in the lung is not carcinogenic in mice Nobody has followed the human influenza lesion past the early stage now we know from mice what to look for While it is hazardous to apply these conclusions from mice to the human I believe taking all things into account we can almost disregard any possible etiological influence of influenza virus in the human lung

Dr Hammond I would like to ask Dr Kretz about his impression from Vienna as to whether the increase in lung cancer is real or due to improved diagnosis It is the same question that was discussed by Dr Steiner and Dr Levin

Dr Kretz The increase of deaths from cancer of the lung is real and absolutely certain Generally the diagnosis is made by the physician who treats the patient The diagnosis of cancer of the lung is mostly verified by biopsy or by clinical examination (X ray bronchoscopy etc) In dubious cases (ill-defined causes of death sudden death etc) a forensic autopsia (« sanitatspolizeiliche Obduktion ») is performed For these reasons the official statistics of the City of Vienna have a high degree of reliability

Dr Doll Have you figures for the consumption of cigarettes in Austria ?

Dr Kretz We have no figures on cigarette consumption because although there is a tobacco monopoly there is a great deal of illegal import of cigarettes and tobacco of very low quality

Dr Clemmesen (Graph indicating comparative figures of cancer in Copenhagen and Vienna cf Clemmesen et al fig 17) It appears that the position in Copenhagen for 1946 to 1950 is almost the same as in Vienna in 1934 Vienna is about 30 years ahead of Copenhagen whatever the reason may be I would like to ask Dr Kretz if tobacco smoking in the form of cigarettes started very early in Vienna and if any information is available when it happened

Dr Kretz Unfortunately I can give you no answer as to the extent of cigarette smoking earlier as the state tobacco monopoly figures are much more recent but I can tell you that also in Vienna youths of 14 and 15 years begin to smoke cigarettes

Dr Levin Have you tried to obtain a history of smoking habits of a group of cancer patients and a comparable group of non cancer patients ?

Dr Kretz This kind of enquiry is being conducted in Vienna but is has only been conducted for five years and it is too early for definite conclusions More important than mortality statistics are morbidity statistics but we have not sufficient information to answer questions I have the feeling that we do not get very accurate information from some of the patients It is just a personal feeling

Dr Hammond I think the suggestion is a good one that we might all undertake here There are differences in the different curves as Dr Clemmesen has shown We have reasonably accurate information on cigarette and tobacco smoking habits It might throw some light on the subject if tobacco has got anything to do with it If the conference thinks it a good idea we might get this information from just a cross section of the different age groups — that would be sufficient

Dr Kretz I think a kind of Gallup poll would give accurate information as to similarities or differences in the habits of people There is a great need for obtaining this kind of information

Dr Stewart Has Professor Kretz noticed an increase in the number of lung cases in autopsies ?

Dr Kretz Also the pathologists of Vienna see an increase of lung cancer autopsies

The degree of the increase is not the same in all institutes This depends on the individuality of the different hospitals to which the institutes of pathology are affiliated So, for example the increase is very high in the institute of Professor Chiari in the General Hospital of Vienna which may be ascribed to the fact that the second surgery clinic of the University is directed by Professor Denk who is very interested in the treatment of cancer of the lung Most lung cancer patients in Vienna are treated in the clinic of Professor Denk Another great hospital of the municipality of Vienna in Wien-Lainz has a great material of lung cancer patients, because Professor Kunz, the chief of the surgical department is also very interested in surgery of the thorax, and there is also a large department for Tuberculosis with many lung patients Many lung cancer patients are primarily diagnosed as having Phthisis In other hospitals of Vienna the increase of lung cancer autopsies is not so high For this reason ... statistics of the pathologists are ... t have the same ... statistics of the City of Vienna

DR SMITH Dr Kretz said in answer to an earlier question that it had not been pos- ... tobacco con- ... war It ... res for ... infor- mation on the amount of tobacco consumed in Vienna in the period 1930 to 1940, or the 1920 to 1930 period ? Also would Dr Kretz comment on the type of tobacco that is used in Austria Does it come from the United States or the Balkans ?

DR KRETZ As far as the kinds of tobacco are concerned in Austria we use cigarettes of our own Austrian tobacco But we have also tobacco from Bulgaria and Turkey, from the United States, and from England As to the second question Professor Denk stated on the Fourth Cancer Meeting 1952 in Vienna that the consumption of tobacco for cigarettes is increasing from 143 gram per year and person in 1923, to 977 gram in 1951 But the period which probably was most important for the increase of lung cancer during the last ten years, namely between 1922 and 1935 began with only a little increase and a clear diminution of the consumption of cigarettes took place between 1929 and 1935

But we have no real proof whether it might be a period of twenty or thirty years or if a much briefer period is sufficient for the development of lung cancer

DR CLEMMESEN I would like to support the suggestions by Dr. Hammond and Dr Levin and I would like to ask if anything is available on the industrial pollution of the air in Vienna, especially with regard to Diesel engines and to the more recent oil industry in Austria near Vienna

DR KRETZ The atmospheric situation has got much worse in Vienna in the last few years and is badly influenced by the traffic, because of pollution of the air by Diesel engines, motor-cars and motor bicycles Another source of smoke is the large number of chimneys in the town During a visit Professor ... said he did not wonder ... in Vie... the lung

SIR ERNEST KENNAWAY By what means is domestic heating carried out and what are the principal industries ?

DR KRETZ Coal and gas — not in open chimneys — there is no burning of wood nor open fireplaces

DR HAMMOND If there is general agreement that we might have a good deal of information about the different graphs shown by getting questionnaires filled in by different countries could it be put on the agenda I wonder ? There are big differences in the graphs One of the possibilities is that it is due to differences in smoking habits It has been suggested that we should get more information on this point from different countries and this would be a very good group to work out a standard method of precision

DR CLEMMESEN On the incidence of can- ... the better we examine ... r in the ... coming ... ood ma- ... phs decline for the highest age classes it is largely artificial and due to the reluctance of doctors to have patients beyond a certain age taken to hospital for troublesome examinations etc

Dr Denoix · With regard to the shape of graphs on age distribution I would like to say that it is extremely important in interpreting the differences which may exist in the form of graphs to take into account the origin of the countries in which these are established as well as the nature of the studies so as to eliminate all possible causes of error or misinterpretation

ZUSAMMENFASSUNG

Es wird die Krebssterblichkeit fur die Atemwege in den Jahren 1910, 1934 und 1951 in Wien verglichen unter Berechnung der Sterblichkeitsrate der verschiedenen Altersklassen und Berechnung von χ^2 Es ist daraus eine betrachtliche Zunahme der Karzinome der Atemwege nach dem 40 Lebensjahre ersichtlich, welche nicht nur die Abnahme der Sterblichkeit an Karzinomen anderer Organe aufwiegt, sondern eine Zunahme der Krebssterblichkeit uberhaupt in Wien zur Folge hat

Bei Frauen ist eine weniger bedeutende Zunahme dieser Krebssterblichkeit bei den Atemwegen nur nach dem 65 Altersjahr feststellbar

Die Prozentzahlen der Karzinome der Atemwege im Vergleich zu anderen Lokalisationen werden fur die verschiedenen Berufe angegeben

SUMMARY

A comparison is made of the mortality from cancer of the respiratory system in Vienna for the years 1910, 1934, and 1951 by computation of mortality rates for various age classes and computations of χ^2 It appears that a considerable increase of carcinomas in the respiratory system has taken place after the 40th year of age which has not only counterbalanced the decline in mortality for cancer of the other sites but has caused a constant increase in mortality from cancer in Vienna

For women a less important increase of cancer of the respiratory system appears only after the 65th year of age

The per cent of cancer of the respiratory system as per cent of all sites is given for various occupations

RESUMEN

Se compara la mortalidad por cáncer del aparato respiratorio en Viena entre los años 1910, 1934 y 1951, computando las cifras de mortalidad segun diversos tipos de edad y computaciones de χ^2 Al parecer se observa un aumento considerable carcinomas del aparato respiratorio despues de los 40 años de edad que no solo compensa el descenso de la mortalidad por cancer de otros organos sino que, incluso ha determinado un aumento constante de la mortalidad por cáncer en Viena.

En cuanto a la mujer se observa un aumento menos notable del cáncer del aparato respiratorio solamente despues de los 65 años.

Se expone el porcentaje de cancer del aparato respiratorio como porcentaje de todos los órganos en relación con diversas ocupaciones

RESUME

Une comparaison sur la mortalite par cancer des voies respiratoires est faite pour Vienne pour les annees 1910, 1934 et 1951 en supputant le taux de mortalite des différents âges, classes et χ^2 On a constaté une tres importante augmentation des cancers des voies respiratoires apres la quarantaine, augmentation qui n'a pas seulement contrebalancé l abaissement de la mortalité par cancer d autres organes mais a causé, à Vienne, une augmentation constante de la mortalité par cancer

Une augmentation moins importante de cancers des voies respiratoires n'apparait, chez la femme qu'après les 65 ans

Le pourcentage des cancers des voies respiratoires comme le pourcentage des autres localisations est donné en rapport avec différentes occupations

RIASSUNTO

Viene compiuto un raffronto della mortalità per cancro delle vie respiratorie in Vienna durante gli [illegible]

della mortalità per cancro

Nel sesso femminile l'aumento meno rilevante del cancro delle vie respiratorie si verifica soltanto dopo il 65° anno

L'A riferisce la percentuale del cancro delle vie respiratorie, come pure delle altre localizzazioni, in rapporto alle diverse occupazioni

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté de faire figurer la totalité des traductions des Résumés

Nous le regrettons et nous en excusons vivement

La Rédaction

MORBIDITY AND MORTALITY FROM CANCER OF THE LUNG IN THE UNITED STATES

BY

Harold F. DORN
(National Institutes of Health, Bethesda, Md., U.S.A.)

During the half century since the death registration area was established in the United States, the recorded mortality rate from cancer has more than doubled, increasing from 64 per 100,000 population in 1900 to 139 per 100,000 . nearly one-half increase in the in the population so that the increase in the risk of dying from cancer, although substantial, was not as great as it appears at first sight

During the first few years of the present century an increase in the mortality rate from cancer took place among both males and females But the rate of increase among white females soon began to diminish and by 1930 had essentially reached zero Since that time the mortality rate for white females has decreased about four per cent after correcting for changes in the age composition of the population Although this decrease is small in comparison with the previous increase, it indicates that the rise in mortality rates from cancer among white females has been stopped

However, the trend in the mortality rate from all forms of cancer among white males is still upward As a result, the risk of dying from cancer now is greater for white males than for white females At the beginning of the century this risk was about 65 percent greater for females than for males , by 1947, due to the continued increase in mortality from cancer among males, the rate for white males was greater than that for white females As yet, there is no clear-cut indication that the cancer mortality rate for white males is nearing a maximum

For several specific forms of cancer, the mortality rate has been decreasing for both males and females Cancer of the skin was the first for which a decline in mortality rates became noticeable At present, the age-adjusted mortality rate for this form of cancer is lower than it was in 1900

The next major group of malignant neoplasms to [illegible] of death pharynx rate has decrease males and females

Mortality from cancer of the digestive tract increased until about 1927 Since that time the age adjusted rate for males has fluctuated about a constant level with no perceptible trend but the corresponding rate for females has declined steadily so that it is now about 15 percent less than it was at its peak This drop in the death rate is the result of a decline in the recorded mortality from cancer of the stomach and liver since the rates for the other major parts of the digestive system, intestines, rectum and pancreas, ha- [illegible]

tality from cancer of the stomach and liver

With the exception of cancer of the uterus and breast, the mortality rate from other major forms of malignant neoplasms still is increasing The greatest relative increase is shown by cancers of the respiratory system of which about 80 percent have their primary location in the lung and bronchus These forms of cancer were reported very infrequently at the time the death registration area was first established in 1900 However since then they have been reported with increasing frequency as a cause of death until at present 9 5 percent of the total number of deaths from malignant neoplasms are attributed to respiratory cancer and 8 1 percent to cancer of the lung and bronchus alone

Cancer of the bronchus and lung is predominately a disease of males *(Table 1)* In both the white and nonwhite population the

TABLE I

Number of deaths from cancer of the lung and bronchus per 100,000 population by age, sex and color, United States, 1930-32, 1939-41 and 1949

Age	White male			White female			Nonwhite male			Nonwhite female		
	1930-32	1939-41	1949	1930-32	1939-41	1949	1930-32	1939-41	1949	1930-32	1939-41	1949
All ages crude	7.3	9.6	19.2	1.9	3.4	4.4	1.2	4.3	10.8	0.6	1.5	2.5
adjusted*	3.7	9.9	18.5	[illegible]	[illegible]	4.2	1.6	5.7	14.3	0.9	2.0	3.3
0-4	0.1	0.2	0.03	0.1	[illegible]	0.1	0.0	0.1	0.0	0.1	0.1	0.0
5-9	0.1	0.2	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0
10-14	0.2	0.2	0.04	0.2	0.1	0.1	0.2	0.1	0.3	0.1	0.1	0.0
15-19	0.4	0.4	0.2	0.2	[illegible]	0.1	0.1	0.3	0.3	0.2	0.3	0.0
20-24	0.5	0.6	0.3	0.7	0.2	0.1	0.5	0.5	0.6	0.2	0.3	0.0
25-29	0.7	0.8	0.5	0.4	0.5	0.3	0.2	1.0	0.3	0.2	0.5	0.1
30-34	0.9	1.5	1.3	0.8	0.7	0.5	1.4	1.6	1.8	0.1	1.1	0.2
35-39	1.8	3.3	4.0	1.0	1.3	1.1	1.1	2.4	6.0	0.8	0.9	1.4
40-44	3.6	7.4	9.6	2.0	2.5	2.4	2.0	6.3	14.2	1.7	2.8	5.7
45-49	6.0	15.6	22.8	[illegible]	4.6	4.6	3.0	10.9	21.4	2.0	4.2	5.0
50-54	8.9	25.0	44.3	4.4	[illegible]	6.9	4.0	18.3	45.5	3.6	5.4	7.8
55-59	11.6	36.6	68.6	6.4	10.2	10.6	6.0	20.0	55.0	2.2	7.7	9.9
60-64	14.9	43.4	88.9	9.0	14.1	15.1	5.6	21.8	64.5	2.4	6.9	10.9
65-69	18.0	42.9	97.5	10.2	16.8	[illegible]	3.4	18.2	58.4	2.6	5.6	15.0
70-74	15.7	39.1	99.4	9.9	18.5	26.9	4.9	17.1	40.4	3.0	6.1	18.8
75-79	14.0	30.0	83.2	8.3	20.0	33.0	4.3	17.3	55.4	1.1	2.3	12.1
80-84	9.4	29.5	71.6	6.0	17.0	32.6	2.1	8.5	14.3	0.0	1.5	14.3
85 and over	7.5	21.5	68.6	5.7	11.0	35.7	2.8	8.9	16.[illegible]	0.0	0.0	11.1

* Age adjusted using the total population of the United States, July 1, 1940
Source National Office of Vital Statistics, U S Public Health Service

mortality rate for males is about 4.4 times the rate for females This differential has more than doubled during the past twenty years due to the more rapid increase of the mortality rate among males

Respiratory cancer is primarily a disease of late adult life (*Figure 1*) It is relatively unimportant as a cause of death prior to age 40 but after that age the death rate rises rapidly reaching a maximum at 70 to 75 years of age among white males after which it decreases again The death rate among white females continues to increase throughout the remainder of the life span It is difficult to judge whether the lower mortality rates among white males over 75 years of age is real or the result of inaccurate diagnosis and reporting There seems to be no reason though why the effect of this latter factor should be greatly different for males than for females

These data also are consistent with the hypothesis that some carcinogenic agent, to which a larger proportion of males than of females are exposed at equivalent doses, has become more prevalent in recent years If this agent were first introduced at the younger ages the consequent increase in mortality might produce a temporary maximum on the age curve of mortality at some point at or beyond the average latent period and before the end of the age span, depending to some extent upon the original shape of the age curve of mortality As persons in the older age groups became exposed to the carcinogenic agent to an extent comparable to younger persons, the temporary maximum on the age curve of mortality would disappear

The temporary maximum on the age curve of mortality would be noticed if death rates were computed for a given calendar data, as are those in *table 1*, since persons of diffe-

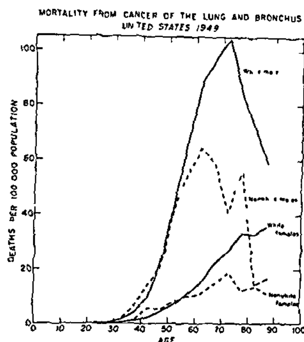


Fig 1

Number of deaths from cancer of the lung and bronchus (Int List Nos 162 163) per 100,000 population by age, sex and color, United States, 1949

rent ages would belong to different cohorts, that is would have different histories of exposure to the carcinogenic agent If the same cohort or group of persons were traced throughout its lifetime, the temporary maximum on the age curve of mortality would not be noticed

Although the data in *table 1* extend over only a twenty year period it is of interest to rearrange them so as to show more clearly the experience of different cohorts The mortality rates for white males appear as follows

Age 1930 32	Mortality rate 1930 32	1939 41	1949
50 54	8 9	43 4	99 4
55 59	11 6	42 9	83 2
60 64	14 9	39 1	71 6
65 69	16 0	39 0	58 6
70 74	15 7	28 5	—
75 79	14 0	21 5	—

The figures along each row are the mortality rates at ages approximately 10 years apart of a group of persons who were all within the same five year age group during 1930-32 For example, the rates on the line opposite the age group, 60 64, in 1930 32, are 14 9, 39 1, 71 6 These are the mortality rates at ages 60 64, 70-74 and 80 84 of persons all belonging to the same cohort When read along rows, all of the above rates increase and do not show the maximum at the age group, 70-74 years, which is seen in *table 1* This suggests that the male age curve of mortality *for a given calendar date* may eventually change its shape and have no maximum prior to the end of the life span

The recorded mortality rates for cancer of the lung and bronchus are about 28 percent higher for whites than for nonwhites This is in keeping with the mortality rates for all forms of cancer which also are higher in the white population The difference is decreasing since the death rate is mounting much more rapidly for nonwhites than for whites and, if the present trend continues, the differential soon will be wiped out

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(Figure 2) In fact, among white males the ... was less

over Even in the nonwhite population where mortality rates from all forms of cancer in ... the decade from 1940 ... decade the ... of the lung and bronchus has been confined to persons over 30 years of age At present then the increase in mortality from this form of cancer is definitely slowing down and is occurring only at the older ages

The most comprehensive morbidity statistics for cancer which can be related to a population base are for Denmark and certain areas of the United States The data for Denmark are from the Danish Cancer Registry ...

tute in 10 large metropolitan area

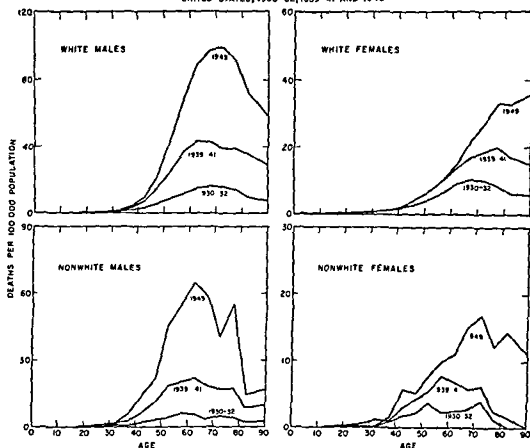


Fig 2

Number of deaths from cancer of the lung and bronchus (Int List Nos 162, 163) per 100,000 population per year by age sex and color, United States 1930 32, 1939 41 and 1949

total population of about 15 million persons The first study by the National Cancer Institute was carried out during 1937-39 and covered all cases and deaths diagnosed during a twelve-months period The study was repeated in the same areas using the same techniques during 1947 and 1948

The reported cases included all of those known to physicians and hospitals In the *first survey 66 percent of the diagnoses of* respiratory cancer and 53 percent of the diagnoses of cancer of the bronchus and lung had been confirmed by biopsy or autopsy In the resurvey these percentages were 75 and 68 respectively

The incidence (new cases diagnosed) of

piratory cancer, namely cancer of the larynx, the ratio of male to female rates is 10 6 or twice as large For males the morbidity rate

TABLE II

Incidence rates (number of newly diagnosed cases) per 100,000 male population per year from respiratory cancer, selected areas of the United States, 1947-48 and 1937-39.

Age	Total respiratory		Bronchus and Lung		Larynx	
	1947-48	1937-39	1947-48	1937-39	1947-48	1937-39
All ages						
crude	38.6	19.7	29.8	11.9	7.2	5.2
adjusted *	38.7	21.7	29.6	13.0	7.4	5.9
0-4	0.2	0.4	0.0	0.0	0.0	0.0
5-9	0.4	0.4	0.4	0.0	0.0	0.2
10-14	0.6	0.2	0.2	0.0	0.0	0.0
15-19	0.4	2.1	0.4	0.4	0.0	0.0
20-24	1.5	0.5	0.6	0.2	0.0	0.2
25-29	2.1	0.9	1.1	0.5	0.0	0.2
30-34	4.1	4.4	2.6	2.2	1.4	0.7
35-39	9.7	7.6	8.3	4.2	1.4	1.5
40-44	22.4	18.3	17.1	11.6	3.9	4.3
45-49	45.1	30.9	37.9	21.1	5.4	5.3
50-54	90.2	53.7	75.0	34.0	13.5	14.6
55-59	157.6	76.3	121.4	45.5	26.6	22.0
60-64	193.1	96.8	146.7	61.0	39.9	24.3
65-69	171.0	94.1	129.7	55.2	40.3	31.4
70-74	181.0	91.7	138.2	51.2	36.0	32.0
75-79	167.2	88.2	111.9	53.3	44.2	26.7
80-84	107.3	72.9	58.3	36.5	33.7	18.2
85 and over	129.7	68.0	91.5	34.0	38.1	34.0

* Adjusted to the age distribution of the total United States population, July 1, 1949
Source National Cancer Institute

TABLE III

Incidence rates (number of newly diagnosed cases) per 100,000 female population per year from respiratory cancer, selected areas of the United States, 1947-48 and 1937-39.

Age	Total respiratory		Bronchus and lung		Larynx	
	1947-48	1937-39	1947-48	1937-39	1947-48	1937-39
All ages						
crude	7.8	4.9	5.9	3.6	0.7	0.4
adjusted *	7.7	5.4	5.9	3.8	0.7	0.4
0-4	0.8	0.0	0.3	0.0	0.0	0.0
5-9	0.0	0.2	0.0	0.0	0.0	0.0
10-14	0.2	0.4	0.2	0.2	0.0	0.0
15-19	0.0	0.4	0.0	0.4	0.0	0.0
20-24	0.7	0.0	0.3	0.0	0.0	0.0
25-29	0.6	0.8	0.3	0.2	0.1	0.0
30-34	1.4	1.2	0.9	0.9	0.2	0.0
35-39	3.4	2.5	1.8	1.7	0.8	0.2
40-44	6.0	5.2	4.4	2.7	0.7	0.6
45-49	11.2	6.8	7.9	4.7	1.8	0.7
50-54	17.7	13.0	14.1	10.7	2.0	0.0
55-59	25.7	19.2	19.9	13.5	2.3	1.9
60-64	29.5	17.5	22.1	13.2	2.2	0.9
65-69	32.4	26.4	23.3	17.8	2.6	2.5
70-74	34.8	26.5	29.6	21.0	1.9	1.8
75-79	34.9	20.8	30.5	17.6	1.1	1.6
80-84	45.9	16.0	43.7	6.4	2.2	3.2
85 and over	42.6	34.5	28.4	20.7	0.0	6.9

* Adjusted to the age distribution of the total United States population, July 1, 1949
Source National Cancer Institute

increases rapidly beginning at about 35 years of age until it reaches a maximum from 60 to 79 years of age after which it decreases (*Figure 3*). The rate for females, on the other hand, increases slowly but steadily until at least 85 years of age. The largest relative difference in the incidence rate for the two sexes occurs at 60-64 years of age when the ratio is about 7 to 1

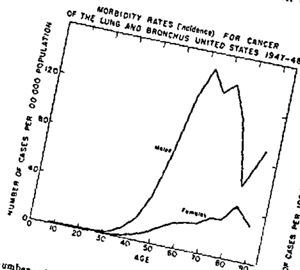


Fig 3

Number of newly diagnosed cases of cancer of the lung and bronchus (Int List Nos 162, 163) per 100,000 population by sex and age, selected metropolitan areas, United States 1949

During the decade from 1937-39 to 1947-48, the incidence rate for all forms of respiratory cancer increased 78 percent for males and 43 percent for females, thus widening the difference between the two sexes For the males, the largest relative increase was for cancer of the bronchus and lung, for females, morbidity from cancer of the larynx increased relatively more than cancer of the bronchus and lung

The morbidity rate for cancer of the bronchus and lung based on diagnosed cases, more than doubled during the ten-year period among males and increased 55 percent among females This increase was restricted to the latter part of the life span, after age 40 for females and age 30 for males

Morbidity from cancer of the bronchus and lung among males is very similar in Denmark and the United States (*Figure 4*) In this connection it should be remembered that the data for the United States are for a population living in large metropolitan areas. The incidence rates for entire Denmark, 1943-47, are about the same as those obtained in the survey conducted in the United States, 1937-39 or about 7 years earlier However the rates for Copenhagen follow those for the United states very closely except for the fact that the maximum occurs about 5 years younger in the Danish data

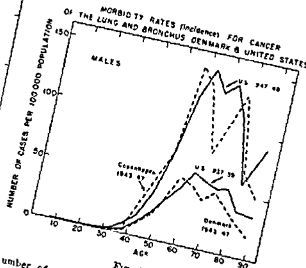


Fig 4

Number of newly diagnosed cases of cancer of the lung and bronchus (Int. List Nos 162, 163) per 100 000 male population by age, selected metropolitan areas, United States, 1937 39 and 1947-48 and Denmark 1943-47

The incidence rate for cancer of the bronchus and lung among females is definitely greater in the data for the United States than it is in those for Denmark, even when the comparison is restricted to Copenhagen (*Figure 5*) On the whole, morbidity from cancer of the bronchus and lung among females in Denmark is more nearly like that found in the first study conducted in the United States during 1937-39

The shape of the age incidence curves for the two sexes changed markedly during the decade between the two surveys. In 1937-39, the shape of the age-incidence curve was roughly similar for each sex, with a maxi-

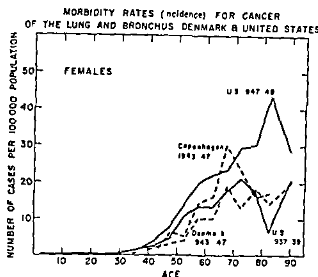


Fig 5

Number of newly diagnosed cases of cancer of the lung and bronchus (Int List Nos 162 163) per 100 000 female population by age selected metropolitan areas United States 1937 39 and 1947 48 and Denmark 1943 47

mum in late adult life followed by somewhat lower rates During the subsequent decade, the peak around 60 74 years for males became much more pronounced while any suggestion of a maximum in the female age curve disappeared, at least prior to age 85

DISCUSSION

DR MORGAN I was very interested in Dr Dorn s figures From an industrial point of view all curves seem to move to the left — they are all exactly the same shape The steeper ones rise to the age group 40 to 45 In our particular industry the peak comes at ages 48 to 50 If it is of industrial origin you get a shift to the left

DR CLEMMESEN Our peak was moving to the left but for the last five years it has started moving to the right again , but I shall comment on these questions in our paper on cancer of the lung in Denmark

DR HAMMOND There is the argument as to whether lung cancer is increasing or not I wonder what Dr Dorn s opinion is on this subject

DR DORN I do not know what one can say It is clear that the amount of diagnosed cases is increasing Anything I would say would be a reiteration of this morning My personal feeling is that many people would not dispute the fact that there has been an improvement in diagnosis That does not mean that there *has not been some real in*crease

DR NEURDENBURG I would like to ask what proportion of deaths were recorded as being due to senility or unknown causes in the United States registration areas

DR DORN Part of the rapid increase in mortality from cancer occurred during the early years of the registration area Quite a bit, undoubtedly, was due to a shift of diagnosis from senility and ill defined causes especially in the group over 60 to 65 years of age and particularly in rural states In general the proportion of deaths attributed to ill defined causes was much higher for the non white population , in some states as many as 25 per cent of the deaths would have been assigned to senility That has decreased It is now in the neighbourhood of 2 per cent for the entire United States

DR DOLL How does Dr Dorn account for the difference in sex ratio which he finds in cities compared with that reported in clinical series ? What does he think one should take as the most reliable estimation of the sex ratio in the States at present ? My inclination is to accept the figures from his survey

DR DORN I am inclined to stick to the figures between 4 and 6 to one You could give all sorts of peculiar sex ratios by taking statistics at individual hospitals The ratio

DR STEWART The superimposition of Dr Dorn s and Dr Clemmesen s curves would suggest that we are dealing with similar carcinogens in widely different geographical areas The logical conclusion is that any genetic factors are overcome by the effect of the carcinogen I find this very surprising

DR DORN I do not know I would suggest that discussion on this point is deferred until we have heard Dr Clemmesen s paper

DR CLEMMESEN I agree However in this connection I would like to point out that the graph for American women is at a higher level than the corresponding graph for Danish women

ZUSAMMENFASSUNG

Se t 1900 le Reg trierung der Todesfälle orga ert wor len war t n U S A le Krebs terl l chke t um 50 % ge t egen obw le Veranderungen n ler Alters erte lung ler Bevolkerung ber ck cht gt s l De Mortal tatsrate be len e sen Fra en erre cl zwischen 19 n l 1930 e n Max mum und sank e t ler um ungefähr 4 % Be den we ssen Ma ern st eg e ununterbrochen an und t nun hol er als be de e ssen Fra en ohne dass s el b s jet t e n Max mum abgrenzen w rde

De Krebssterl l chke t be erschie lenen Ha ptgru pen von mal gnen Geschwul en st n a m R ckgang begriffen Unter le en f gurieren le Karz nom ler M n lhol le n l d s Pharynx der Ha t de Verla ngstraktes un l des Uterus De Mortal tat le Mam nakarz noms lagegen ze gt ke ne esentl che T le y zur Abnahme o l r z r Zunahme Be anderen Haupt gruppen on Karz nomen ze gt le M rtal at mm r noch e ne Z nahme De grosste relat e Z nalme w rd beo achtet be Karz nomen der Atem ege wo be n ungefahr 80 % der Pr mar mor n len Bron l en und der Lunge l egt

So ohl in der we sen w e n ler farl gen Be l kerung ist de Mortal tatsrate be m Bron h s n l Lungenkarz nom f r le Manner ca 4 4 mal gro ser als f r le Fra en Ausserdem noch ladurel gros er lass le mannl che Mortal ta r l ese D ffer ra e we terl n anste gt Wahren l der Dekad 1940 19 0 war le Z nahme l r Mortal ta srate ler Bron ch s n l L ngenkarz nome nur halb so gross als n ler orhergehenden Dekade Be den Frauen nalm s e nur z be h herem Alter als 55 Jal re be len M n nern rde e ne Z nalme be allen Altern ber 3, Jalre regi r rt

De Krebs terl l chke tszahlo de on Nat onal ancer In t tute n d r Ze t on 193 39 nd 194 48 n zehn a sgew l l en Gros tadtzon n l r U S A gesammelt w r l waren be at gen lese Schl fol gerungen Na h l n ne e t n Fest el ngen werd n Manner f nf mal ha f ger on Lungenkrel s befall als Fra en In lessen s n l le Untersch ele zw schen len Ge chlechtern be m Larynxkarz nom sogar noel grosser wobe de mannl che S erl ichk t rate 10 6 mal d e we bl che ubertrifft Ih loppelt so gross t al be m L ngenkarz nom Be Mannern erre cht sie las Max mum zw sel en 60 und 9 Jahren wal ren l le Fra en e n kont n erl her A t eg l s m n l ns 8 Jahr z sehe t

In Danemark st le Ha f gk t l r Lu gen n l Bron h alkarz nome m Ze traum 1943-47 l gl che w e l e jen gen n len U S A o 193 39 Da de Angaben a U S A s Gros a l en stamme n l eler m t l njen gen a s Kopenhagen al a ganz Danemark z ergle cl en Ueberrasel en l n e s nd le Haaf gke szahlen be Man ern n K pen l a gen genau gle l e n U S A in der Ze t von 194 48 Der ha ptsa hl cl te Untersel e l be tel t lar n lass be len D nen las Max m m m Alter on b s 59 Jal ren auftritt oder ungefal r f f Jahre fr her als n U S A Be len Frauen jedoel ist le Mort l tat fur Lungen un l Bronch alkarz nom so ol l n K pen hagen e auel n ganz Danemark l rjen gen 193 39 in U S A gef n len n al nl ch

SUMMARY

Mortal ty fro n cancer n tle U ed States n rease l about 50 per cent aft r a lju t ng for cl ges n tle a e l tri t on of the pop lat on s n e tle l ath regi trat on area was organ 1 1900 The leath rate among wl e f males rea hed a max m bet een 1925 an l 1930 an l s nce that t me has l ereasel about fo r percent Tle r e f r wl te ma s has cont ned to crease a l h le rate for h te females w tl o clear e t nd cat on tlat t s nearing a max m n

Mortal ty from ca cer of se eral major gr ps of r al gnant neop asm s s no leer as ng Among these are cancers of the buccal ca t a l plarynx sk n l ge t e tract an l uterus In a l l t on mortal ty from cancer of the breast shows no s gn f cant p ar l or lo nward tren l How er mortal ty fro n other maj r forms of cancer is st ll ncrea ng tle greate t rela t e ncrease is f r can ers of the re p ratory sy t m of wh ch about 80 per cent ha e tl r primary loca t on n the bronel and l ngs

In bo l the wl te an l non l te popu at o s the leatl rate from a cer of the l ng an l bronel s f r males s abo t 4 4 t mes tlat for f nal s More r th s d fferent al s becom ng great r lue to the more rap d ncrease of tle male mortal ty ra e Dur ng the leca le from 1940 to 1950 the rate of ncrease in mor tal ty from cancer of the lung an l bronel u was nl one half that of tle pre io s leca le Am ng femal s leatl rates ncreasel nl at ages abo e ears among ma es an crease was recorded at all ages abo e 35 years

Can er morb l t lata coll c ed b tle Nat onal Cancer Inst tute luring 1937 39 and 194 48 n ten large me ropol tan areas n tle Un ted Sta es conf rm l ese con lusions The nc lence (new l agnosel cases) of cancer of the l ng s f e t mes as great among males as among females How er the sex d fferent al for laryngeal cancer s e en greater tl rat o of male to f male m rt l ty rates be ng 10 6 or t ce as large For males the nc lence ra e reaches a max mum from 60 t 0 ears of age but f r females the rate n reases nt l at l a t 8 ears of age

Inc lence rates f r cancer f tle la a l l ron l s for D nmark 1943-4 are s m lar to those ob ta ned in the morb d ty stu ly of 193 39 n the Un ted Sta es S nce the lata f r the Un ed S ates are

from metropolitan areas a more appropriate compa

States, 1947 48 The primary difference is that the maximum for the Danish data occurs during ages 55 to 59 or about five years earlier than in the data for the United States For females though, morbidity from cancer of the lung and bronchus in Copenhagen as well as for all of Denmark is more nearly like that found during 1937-39 in the United States

RESUMEN

Desde que existe en los Estados Unidos un registro de la mortalidad, o sea desde 1900, la mortalidad por cancer, teniendo en cuenta las variaciones de la distribucion por edad de las poblaciones ha aumentado en un 50 %

La cifra de mortalidad por cancer en la mujer blanca ha alcanzado un máximo entre 1925 y 1930 y desde entonces ha decrecido en un 4 % aproximado La cifra de cánceres para el hombre blanco ha seguido creciendo y alcanza actualmente una cifra mas elevada que para las mujeres blancas sin indicacion clara de llegar al máximo

La mortalidad por diversos cánceres importantes por su frecuencia está actualmente en descenso Debemos citar entre estos los canceres de la cavidad bucal de la faringe, de la piel, del aparato digestivo y de la matriz Ademas la cifra de los canceres de mama no ha cambiado de manera significativa La mortalidad por otras formas de canceres importantes sigue siempre aumentando y el aumento relativo es mayor para el cancer de las vias respiratorias y de estos el 80 % se originan en los bronquios o en el pulmon

Tanto en los negros como en los blancos la mortalidad por cancer pulmonar es aproximadamente 4 4 veces mas elevada para el sexo masculino que para el femenino Esta diferencia se acentua por el hecho del aumento de la mortalidad en el hombre Durante el transcurso del decenio comprendido entre 1940 y 1950 el aumento de la mortalidad por cancer pulmonar y bronquial solamente fue la mitad de la observada en el decenio precedente El aumento no se observa en la mujer sinopasados los 55 años en tanto que en elhombre este aumento se observa en todas las edades por encima de los 35 años

Los adtos de mortalidad por cancer recogidos por el Instituto Nacional del Cancer durante 1937 39 y 1947 48 en diez arez extensas metropolitanas de los Estados Unidos confirman estas conclusiones La frecuencia (casos diagnosticados recientementes) del cancer pulmonar es cinco veces mayor en los varones que en las mujeres Sin embargo la diferencial del sexo en el cancer larigeo es incluso mayor siendo la proporción de morbilidad entre el hombre y la mujer como 10 6 o dos veces mayor En los varones la fre

La frecuencia de cancer de pulmon y bronquios en Dinamarca (1943 47) es similar a la observada en el estudio de morbilidad de 1937 39 en los Estados Unidos Como los datos de los Estados Unidos corresponden a areas metropolitanas la comparacion mas apropiada es con Copenhague y no con toda Dinamarca Las cifras de frecuencia en los varones en Copenhague son sorprendentemente similares a las de Estados Unidos (1947 48) La principal diferencia consiste en que el maximo en los datos daneses tiene lugar durante las edades 55 a 59 o unos cinco años antes que en los datos norteamericanos Sin embargo en la mujer la morbilidad por cancer pulmonar y bronquial en Copenhague y en toda Dinamarca es mas semejante a la observada durante el periodo 1937 39 en los Estados Unidos

RESUME

Depuis qu il existe aux Etats Unis un enregistrement de la mortalité soit, depuis 1900, la mortalite due au cancer, tenant compte des variations dans la distribution d âge des populations est accrue d environ 50 %

Le taux de mortalité due au cancer chez la femme blanche a atteint un maximum entre 1925 et 1930 et depuis lors elle a decru d environ 4 % Le taux de cancers pour les hommes blancs a continué a croître et atteint actuellement un taux plus élevé que pour les femmes blanches sans indication nette d approcher un maximum

La mortalité due à plusieurs cancers importants par leur fréquence est actuellement en décroissance Il faut citer parmi ceux ci, les cancers de la cavité buccale du pharynx, de la peau du tube digestif et de l utérus De plus, le taux des cancers du sein n'a pas change de façon significative La mortalité par d autres formes de cancers importants est toujours en augmentation l'augmentation relative etant la plus grande pour le cancer des voies respiratoires et parmi ceux ci, 80 % prennent naissance dans les bronches ou dans le poumon

Chez les hommes de couleur comme chez les blancs la mortalité due au cancer du poumon est d environ 4 4 fois plus elevée pour les hommes que pour les femmes. Cette différence s accentue du fait de l accroissement de la mortalite chez les hommes Au cours de la decade comprise entre 1940 et 1950 l accroissement de la mortalite due au cancer des poumons et des bronches ne fut que la moitie de ce que l on avait observé au cours de la decade précédente L augmentation ne s'observe chez la femme qu'après l age de 55 ans tandis que chez l homme, elle se manifeste a tous les âges

Les chiffres donnés concernant la morbidité cancereuse rassembles par le N C I de 1937 à 1939 et de 1947 a 1948 dans 10 grandes regions metropolitaines en U S A confirment ces conclusions L'incidence des nouveaux cas de cancer du poumon diagnostiqués est de 5 fois plus élevee chez les hommes que chez les femmes Pourtant cette différence entre sexes est en

core pl s marquee pour le ca cer d lary x l raj port le la frequence le morl l te entre les l n et les femmes etant le 10 C s t le lo l le le ce q o obser e pour le cancer l poumon Cl z l lomm l ne denc atte nt le max m m le 60 a 9 ans tan l que chez la femme l ne l ce co t n e a s a ero tre au moins jusqu à l ge le 8 an

La pause les ne le c s l s ca cers l poumo et les bronel s calculee au Danemark de 1943 à 1947 est comparable a celle le la morb d te ét d e e U S A pour les années allant de 1937 à 1939 Ma s comme les lonnees américa nes ont e rassemblees lans les v lles metropol ta nes la compara son le ra t plutot se fa re a ec C j enl agi e qu a ec l ent er te l royaume

I ne lence mascul ne des cancers du po non est tonnamment superposable à celle observée en U S A de 1947 à 1948 La d fference essent elle res le dans le fa t q a Danemark l ne lence max male s obser e entre 55 et 59 ans so t en ron 5 ans pl s tard q en U S A Neanmo ns la morb dite f m n ne en ce q concerne le can er l po mon et les bronches est elle auss tres o ne pour Copenhague et po r l ensemble du Danemark de ce q a été décrit pour les Ftats Un s d Amériq e po r la periode le 1937 à 1939

RIASSUNTO

Negl Stat Un t dopo la st tuz o e lella d nunc a lella mortal tà a venuta nel 1950 la mortal tà p r cancero r s lta aumentata d c rca 1 50 % tenen lo con to delle variaz on nella l tribuz one l ll et

La percentuale l mortal tà do ta al cancero ella l n a l razza b a ca ha raggiunto l mas n tra l 19 e l l 1930 e da tale epoca è l m nu to l c rca l 4 % mentre la perc ntuale nel esso masel le l razza l anca ha cont ato a l a mentare e raggi nge att almente una percent ale j ele ata el n l a lonna, d lla stessa razza senza el ara n l caz one di aver raggiunto l ma mo La mortal tà l ta a va rie forme d tumori mal gn è ora n l m nu one Tra q e se no caneri l lla cav à boccale d l fari ge l lla e te l l t bo l gerente e l ll u ero Inoltre l cancro della mammella non l mostra ariaz o sen s l l

La mortal tà per le altre forme p à freq ent l cancero è t ttora n a mento e l aumento relat vo e magg ore per il cancero lelle vie resp ratorie e l q est l 80 % pren le origine da bronch o dal polmone

Nella popolaz one masch le di razza b anca o d c l re la mortal tà do ta a cancero del polmone e d c rca 4 4 vol e j ele ata nel sesso masel le el e n l se so femm n le Tale l fferenza s accent a per il j rap lo aumento lella mortal ta nel sesso ma ch le Nella lecale 1940 19 0 l aumento della mortal tà per cancero lel polmone e le bronch non f che la meta co fro to alla l ca l j recede e L a m to no s o s r a nella lonna lopo l eta l 5 a mentre s man festa nell uomo d q al a eta

Le c fre riferite che riguardano la mortal ta per t m ri raccolta dall I t tuto Naz onale lel Cancro negl anni 1937 39 e 1947-48 n 10 gran l centri legl Stati Un t c nf rmano q s e conclu on

La fr q enza l ca l cancero lel polm e l ag no t cati per la pr ma v lta e d 5 ol e p u ele ata nell uomo in confronto alla lonna. T ttora questa d fferenza in rapporto al sesso e p elevata per il cancero l l laringe essen lo il rapporto l frequenza nella mortal ta tra l uomo e la lonna l 10 C c oè l lopp o l quanto s osserva el cancer lel polmone Nell om la frequenza ragg nge l ma mo tra 60 79 ann mentre nella donna la freq enza cont n a a l aumentare f no all 8 anno

I arre to nella frequenza lel cancero broncopolmonare val tata n Dan marca nel periodo 1943 1947 è confrontab le a quella l lla morb l tà st l ata negl Stat U n t l rante gl ann 193 1939 F sen lo i lat ameri an raccolt nelle c ttà l confro to s le e fare con Copenhagen p tto t el e con t tto il regno

La freq enza osservata i el sesso masel le è s ra r l nariamente so rappon b le a quella as nta negl Stat U n t dal 1947 al 1948

La l fferenza fon lamentale e do nta al fatto el e n Dan marca la freq enza mas ma s osserva n l perio lo 55 59 ann c oè c rca 5 ann p tar l el e negl S at U n t mentre la mort l tà f mm n l per q ant riguarda l cancero l ro copolmonare è per Copenha gen e p r tutta la Da marca mo s na a q lla r contrata negl Stat U n t l rante l periodo 193 1939

Il ou a été mp ble j a si e le rco a lépe la tes le o e r até de fa e f que e l to a té les t a lu t on les Résumés

Nous le regrett n et on e excu ons r re n ut

La Réla t on

UNE OPINION BELGE SUR LA FREQUENCE ET L'ETIOLOGIE DU CANCER PRIMITIF DES BRONCHES

PAR

Ch DE MUYLDER
(Universite Catholique de Louvain Belgique)

Comme en beaucoup d autres pays on repete en Belgique que le cancer du poumon augmente de frequence et que cette fréquence accrue est attribuable a la consommation excessive de cigarettes (cancer du fumeur de cigarettes *specialement celui qui inhale la fumee*)

Que reste t il de cette affirmation apres une analyse objective ?

Il importe de definir le sujet nous envisageons les cancers bronchiques se developpant aux depens de la muqueuse des bronches et bronchioles a toutes fins pratiques nous nous contentons des types histologiques suivants

[162 1] a) carcinome epidermoide (epithelioma epidermoide)

b) carcinome anaplastique (epithelioma anaplastique ou carcinome a grandes cellules ou a petites cellules ou « oat cell carcinoma »)

c) adénocarcinome (epithelioma glandulaire)

exclut

e) les tumeurs a cellules alveolaires (carcinome bronchiolaire?)

f) les adenomes bronchiques malins (?)

g) les tumeurs malignes a type « glandes salivaires »

h) les soi disant sarcomes et autres raretes

La frequence de ces *tumeurs a t elle* augmente dans la population belge ? Au point de vue statistique il faut distinguer entre la *morbidite* et la *mortalite* si cette distinction a de l importance pour certains cancers tels les cancers cutanes elle est depourvue d interet pour les cancers pulmonaires l immense majorite des malades meurent endéans l annee qui suit le diagnostic (survie moyenne de 5 *mois* cfr VAN GOIDSENHOVEN et DE GRAEVE)

Peuvent provoquer une difference entre la morbidite et la mortalite 1) les cas gueris par la chirurgie mais leur nombre est très petit 2) les cas freines par la radiotherapie au point qu un autre diagnostic est pose au *moment* de la *mort, p ex* decompensation cardiaque hémorragie cerebrale etc ces cas sont également peu nombreux

La cause d erreur la plus grossiere dans *notre pays* est *l impossibilité de determiner* surement la cause du deces pour l ensemble de la population les certificats de déces portent mention de l accident final banal et non pas de l entite morbide ils constituent dans le cas qui nous occupe autant de réponses a la question que nous posait un *etudiant* « Mais de quoi meurent en fait les

que le cancer est une maladie inavouable On a suggere que dans notre pays on change la forme du certificat de déces un triptyque serait forme de deux volets portant les ren

pareille a ...

National d Assurance Maladie Invalidité et *est utilisee* partout avec satisfaction (voir exemplaire annexe)

Ceci explique pourquoi il n y a pas de statistique nosologique valable sur le plan natio

Fonds National d Assurance Maladie Invalidité

DEMANDE D AUTORISATION DE SEJOUR

MALADE TITULAIRE

Nom

Prénom

Adresse

ORGANISME ASSUREUR (Mutualité ou Fédération)

Indice Statistique

Etablissement hospitalier

Service Salle Lit

Date d entrée

(Fiche à renvoyer à l organisme assureur (Mutualité ou Fédération dont question ci-dessus) avant l expiration du 2e jour en cas d hospitalisation pour traitement ou avant l expiration du 6e jour en cas d hospitalisation pour mise en observation)

Date

Le Directeur de l'Etablissement

N° 608455

Avis du Médecin Conseil

N° 608455

Raisons qui justifient la prolongation de la mise en observation au-delà de 7 jours :

Durée totale probable de la mise en observation

mise en observation

Affection pour laquelle le malade est hospitalisé :

Traitement institué ou à instituer

Durée probable de l'hospitalisation pour traitement

traitement

Le Médecin traitant

Date

Fig 1

nal, en utilisant les declarations médicales de décès Nous avons contrôle ce fait personnellement Les services gouvernementaux peuvent nous fournir, pour l ensemble du pays, un seul elément de base solide la mortalité generale, et la mortalite par cancer (telle qu'elle est declarée), par sexe , par exemple en 1950, il y a eu 106 880 decès, dont 56 668 hommes et 50 212 femmes , pour la

parément, pour les deux sexes reunis et le taux annuel pour 100 000 personnes (p 25) Les courbes de mortalité pour chaque sexe sont à peu pres paralleles et, par conséquent ne montrent pas l accroissement relatif des cancers chez les mâles humains observé dans d autres pays et attribuable en partie aux cancers du poumon *(voir graphique II p 143)* C est le seul renseignement que nous puissions tirer de ces donnees Pour savoir si le cancer bronchique est en augmentation réelle il faudrait au moins avoir le nombre de ses victimes annuelles rapporté a la population totale du royaume par groupes d ages de 5 ans s etendant jusqu'a l extreme limite de longevite en Belgique les différences raciales sont de plus en plus negligeables, et l exiguite du territoire assure une constance suffisante des conditions geographiques

Si la mortalité generale par toutes tumeurs malignes a presque triple en Belgique depuis *un demi siecle (59/100 000 en 1903, contre* 116,1/100 000 en 1950) le role de la « conscience du cancer » dans cette multiplication est impossible a déterminer

* * *

Nous avons obtenu des renseignements fragmentaires par le « Bulletin de statistique du Royaume de Belgique » (mai 1937, et numeros suivants)

La mortalite déclarée, par affections cancereuses de l appareil respiratoire dans les grandes agglomerations était la suivante en 1936, 1940, et 1941

Années	Anvers H.	Anvers F.	Bruxelles H.	Bruxelles F.	Gand H.	Gand F.	Liège H.	Liège F.	Total H.	Total F.
1936	19 6.7 %	6 1 6 %	39 7.5 %	11 1 6 %	3 1 8 %	4 1.7 %	12 6 3 %	0 0 %	73 6.2 %	21 1 4 %
1940	14	11	78	23			23	4	115 9 02 %	38 2 66 %
1941	29	13	78	26			25	3	132 10 07 %	42 2.65 %

Les décès par cancers de l'appareil respiratoire dans les communes de plus de 20.000 habitants étaient les suivants pour six années ultérieures :

Années	Communes de plus de 20 000 h. H.	F.
1942	207	48
1943	228	65
1944	169	43
1948	301	78
1949	377	92
1950	424	91

C'est en nous servant de ces deux tableaux que nous avons construit le graphique III

précis sur le

nes adressé à diverses organisations de secours et d'assurances ; les chiffres devraient être d'autant plus fidèles que les malades ont un intérêt matériel à se faire connaître.

Nous avons songé d'abord à ce groupe très intéressant des anciens combattants de la guerre 1914-1918, qui sont maintenant à l'époque de la plus grande fréquence du cancer, qui comprennent une très grande proportion de fumeurs de cigarettes et de bronchitiques chroniques ; nous espérions aussi trouver l'un ou l'autre cas de cancer du poumon traumatique, ou soi-disant tel. Nous avons interrogé un spécialiste de l'Oeuvre Nationale des Invalides de Guerre, qui nous a affirmé qu'il n'existait de ce côté aucune possibilité de travail pratique.

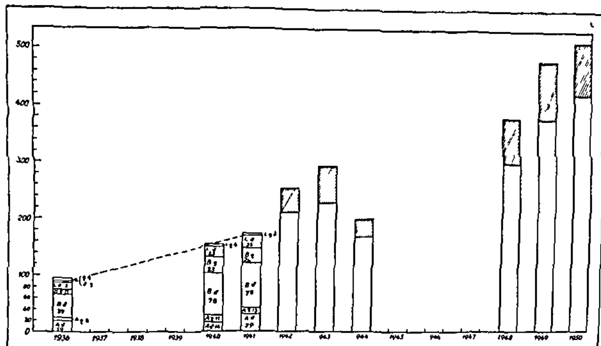
L'Office Médico-Légal ne possède pas non plus de documentation utilisable.

Il n'y a pas de statistique utilisable provenant des Compagnies d'Assurances.

L'Oeuvre Nationale Belge de Lutte contre le Cancer ne peut nous fournir que les publications classées dans sa bibliothèque.

Finalement ce sont les mutuelles qui nous ont fourni les renseignements les plus pré-

	Groupe 1 (C) C. = 1.250.000 H.	F.	Groupe 2 (S) S = 1.000.000 H.	F.	Groupe 3 (N) N. = 350.000 H.	F.	3 groupes H.	F.	2 sexes	♀ en % du total
1949			104	7	34	4	138 2 groupes	11	149	7.38 %
1950	52	8	140	10	39	3	231 3 groupes	21	252	8 33 %
1951	74	8	170	9	37	0	281 3 groupes	17	298	5.7 %



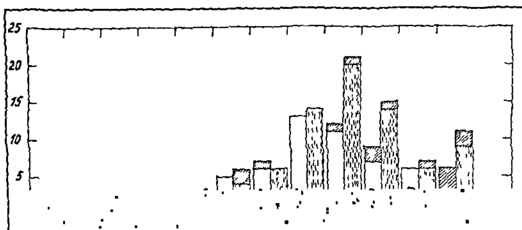
Graphique III

Mortalité par affections cancéreuses de l'appareil respiratoire dans les grandes agglomérations en 1936 Anvers, Bruxelles, Liège et Gand

1940)
1941) Anvers, Bruxelles, Liège

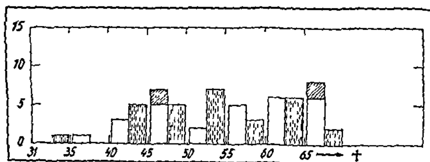
Décès par C de l'appareil respiratoire dans les communes de plus de 20 000 habitants, à partir de 1942 *(en hachures, les décès du sexe féminin)*

Femmes 1950 ou 1951  Hommes 1950  Hommes 1951 

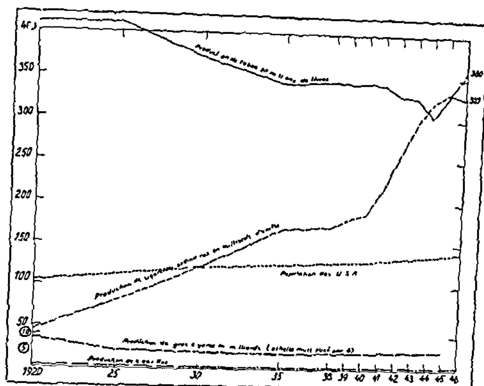


Graphique V
Nouveaux C bronchiques classés par années d'âge et par sexe
Total (1950) 52 ♂ & 8 ♀ = 60
(1951) 74 ♂ & 8 ♀ = 82

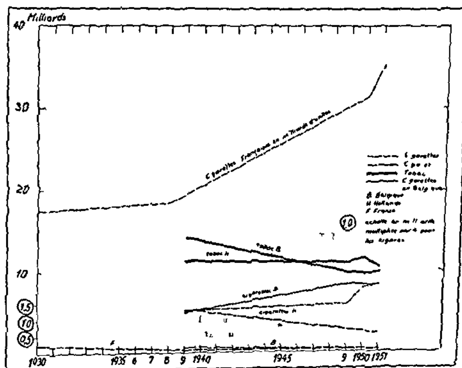
142 cas



Graphique VI
Cancer du Larynx



Graphique VII



Graphique VIII

I want to point out that it is a very recent habit in Belgium for women to smoke and even now only few women do

SIR ERNEST KENNAWAY Has Professor Maisin ever seen a case in a non smoker ?

DR MAISIN Among men ? Never

DR DE MUYLDER In a limited inquiry about the incidence of the condition among nuns we have not found a single case

SIR ERNEST KENNAWAY In Canada where there are many nuns there has never been any case among them of cancer of the lung

DR MAISIN It would be very interesting to make a study among nuns In general they live in a smoke free environment whereas women living with their husbands do not — even if they are non smokers themselves

With regard to cancer of the cervix in 2000 cases treated in this institute I have never seen a case in a nun who had not been married before entering the church These figures are based on clinical records, not autopsies

SIR ERNEST KENNAWAY Do the nuns come for treatment ?

DR MAISIN Oh yes

DR CLEMMESEN The reason that we do see some cases of cancer of the lung among non smokers is probably that such cases are at least largely adenomatous cancers while the cases caused by smoking are — at least largely — non adenomatous forms Correspondingly, when cervical cancer occurs in virgins or children it may be adeno carcinomas and it would therefore also be interesting to see if possible cases among nuns are not adeno carcinomas

DR KUSCHNER Has Dr Dorn an information on the incidence of cancer of the lung in communities with what might be a lower incidence of smoking, such as Salt Lake City?

DR DORN We have no morbidity information for Utah However, last summer, 1951, we undertook a morbidity study of cancer in the entire state of Iowa which is a rural state with a large farm population The results of this study are not yet available, but we are looking forward to comparing these data with those from our studies in metropolitan areas If these data should be similar to those for Denmark I expect that the morbidity rate for lung cancer in Iowa will be less than the corresponding rate for the metropolitan areas

DR HAMMOND The Utah death rates are slightly below those for the rest of the country, but we have no information on incidence

ZUSAMMENFASSUNG

Der Verf bespricht die verschiedenen Informationsquellen uber die Haufigkeit des Lungenkrebses in Belgien Obwohl es unmoglich ist einen genauen mathematischen Beweis uber die Zunahme der Haufigkeit zu liefern scheint das medizinische Problem des Lungenkrebses beim Menschen von Tag zu Tag wichtiger zu werden Die Zahl der Todesfalle an diesem Karzinom nimmt in verschiedenen Stadten zu, ebenso in den Universitatskliniken von Louvain und bei den Versicherungen Es werden genaue Angaben uber die Altersverteilung und den Tabakverbrauch gegeben

SUMMARY

The author surveys various sources of information on the frequency of cancer of the lung in Belgium While he is unable to give a strictly mathematical proof of an increase in frequency it appears that the importance of cancer of the lung among men is increasing as a practical medical problem The number of deaths from cancer of the lung among men is increasing in various towns in the clinic of the University of Louvain and in the trade unions Details on the distribution by age of cases are given together with figures on the consumption of tobacco

RESUMEN

El autor pasa revista a las diferentes fuentes de informacion sobre frecuencia del cancer del pulmon en Belgica Aun cuando no pueda proporcionar una prueba matematica exacta del aumento de la frecuencia es de opinion que el problema medico del cáncer de pulmon en el hombre se hace cada dia mas importante el numero de muertes por cancer pulmonar en el hombre aumenta en diversas ciudades en las clinicas universitarias de Lovaina y en las sociedades mutuas

La comunicacion contiene detalles sobre la frecuencia en funcion de la edad y cifras sobre el consumo de tabaco

RESUME

L'auteur passe en revue les différentes sources d'information sur la fréquence du cancer du poumon en Belgique. Tout en étant incapable de fournir une preuve mathématique stricte de l'augmentation de fréquence, il lui semble que le problème médical du cancer du poumon chez l'homme devienne de jour en jour plus important. Le nombre de décès par cancer du poumon chez l'homme augmente dans diverses villes, aux cliniques universitaires de Louvain, et dans les mutuelles.

Le rapport comporte des détails sur la fréquence en fonction de l'âge, et des chiffres ayant trait à la consommation de tabac.

RIASSUNTO

L'A. passa in rassegna le differenti fonti di informazione sulla frequenza del cancro del polmone in Belgio. Pur non essendo in grado di fornire una dimostrazione matematica sull'aumentata frequenza di tale affezione, è indotto a ritenere che il problema del cancro del polmone nel sesso maschile sta divenendo, dal punto di vista pratico, sempre più importante. Il numero dei decessi per cancro del polmone nel sesso maschile è in aumento in diverse città, nelle cliniche universitarie di Lovanio, come pure nelle organizzazioni mutualistiche.

Vengono forniti dettagli sulla frequenza del cancro del polmone in rapporto all'età, e le cifre che si riferiscono al consumo del tabacco.

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Resumés.

Nous le regrettons et nous en excusons vivement.

La Rédaction

LES CANCERS BRONCHO-PULMONAIRES EN FRANCE ENTRE 1946 ET 1951

PAR

P F DENOIX

(Chirurgien des Hôpitaux de Paris
Directeur de la Section du Cancer à l'Institut National d'Hygiène Paris France)

Il est difficile de se faire une idée exacte de l'augmentation du cancer du poumon en France de 1940 à 1950

Les deux sources qui permettraient d'apprécier l'importance de cette augmentation seraient d'une part les déclarations de décès et d'autre part une enquête géographique permettant d'établir un taux de fréquence basé sur la morbidité

— Une enquête géographique sur la fréquence des cancers a débuté en France le 1er janvier 1951 il est trop tôt pour en connaître les résultats

— L'étude des déclarations de décès présente des difficultés du fait que d'une part de 1940 à 1946 les perturbations dues à la guerre rendent la documentation sans valeur d'autre part ce n'est qu'à partir de 1950 que l'on a isolé les cancers trachéo broncho pulmonaires — n° 49 de la Liste en 200 causes de la Nomenclature Internationale 1948 — alors qu'avant cette époque l'ensemble des cancers de l'appareil respiratoire était groupé sous le n° 47 de la nomenclauture 1938

Pour essayer de pallier cet inconvénient nous avons eu recours à l'artifice suivant

TABLE I

CANCER BRONCHO PULMONAIRE DEPARTEMENT DE LA SEINE

Taux de décès pour 100 000 habitants de chaque tranche d'age

SEXE MASCULIN

Ages	1946	1947	1948	1949	1950	1951
0 4	—	2 4	—	0 8	0 8	—
5 9	—	—	—	—	—	—
10 14	—	—	—	0 8	—	—
15 19	0 7	0 7	0 7	1 4	—	—
20 24	0 6	1 2	1 2	—	0 6	0 6
25 29	3 1	1 5	0 8	2 3	3 1	1 5
30 34	1 1	1 1	1 7	1 1	1 7	2 8
35 39	4 3	3 9	5 3	4,3	4 3	4,3
40 44	16 5	19 7	15 1	1 9	8 7	9 2
45 49	19 9	30 5	24 7	14 2	33 1	37,3
50 54	2,2	10 4	30,3	45,9	60 7	72 5
55 59	27 9	28 9	8 7	38 4	71 5	87 2
60 64	25 5	59 2	66 1	89 3	96 3	90 4
65 69	33	44 6	85 9	117	138 7	145,2
70 79	1 8	18 1	12 6	69 6	119 2	139
80 et plus	—	12	48 1	72 2	84 2	108
Total	8	12 7	13 5	18 4	25 4	27 9

NB De 1946 à 1949 il s'agit des taux calculés d'après les nombres estimés (voir texte) en 1950 et 1951 les taux sont calculés d'après les décès rangés sous le n A 50 de la Nomenclature Internationale (1948)

FRANCE ENTIERE

TABLE II

CANCER BRONCHO PULMONAIRE

Taux de deces po r 100 000 habitants de chaque tranche d âge

SEXE MASCULIN

Ages	1946 Taux brut	1947 Taux brut	1948 Taux brut	1949 Taux brut	1950 Décès déclarés	1950 Taux brut
0 4	0 0	0 3	0 06	0 1	°	0 1
5 9	—	0 15	0 15	0 °	4	0 3
10 14	0 07	—	—	0 06	1	0 07
15 19	0,3	0 5	0 4	0 3	5	0 3
°0 °4	0 34	0 34	0 4	0 34	7	0 4
5 °9	0 64	1 14	0 04	1 °4	10	0 6
30 34	0 7	0 7	1	0 5	1°	1 3
35 39	° °	1 8	° 7	1 7	3	° 1
40 44	6 8	7	6	6 7	91	5 9
45-49	8 7	15 5	17 9	1 9	°40	15 9
50 54	6 9	10 5	°0 3	31 ,	374	30 6
55 59	10	18 1	°1 6	°7 5	405	43 5
60 64	13 9	°3 1	8 4	36 3	431	50,5
6, 69	15 4	°1 7	36 9	39 7	416	58 6
0 79	15 7	3° 8	3	43 °	70 74 345	59 4
					75-79 167	47
80 et plus	,4	8 8	° °	27 8	80 84 60	4° 5
					85 & + 13	°°
					Age Inc 1	
Tous âges	4	6 6	11 9	9 8	° 616	13 1

N B De 1946 à 1949 il s agit des taux calc lés d après les nom l res est més (o r texte) en 1950 les taux sont calculés d après les décès rangés sous le • \ 0 de la Nomenclature Internat onale (1948)

FRANCE ENTIERE

TABLE III

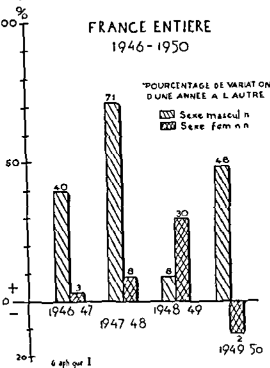
CANCER BRONCHO PULMONAIRE

Taux de decès pour 100 000 hab tants de chaque tranche d age

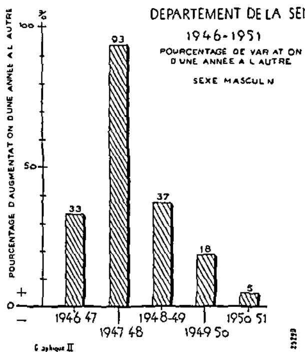
SEXE FEMININ

Ages	1946 Taux brut	1947 Taux brut	1948 Taux brut	1949 Taux brut	1950 Décès déclarés	1950 Taux brut
0-4	0 07	—	0 06	0 05	°	0 1
5 9	0 15	0 07	—	—	—	—
10 14	0 13	0 07	0 °	—	°	0 1
15 19	0 4	0 °	0 1	0 5	°	0 1
°0 4	0 4	0 5	0 3	0 1°	°	0 1
5 °°	0 61	0 4	0 44	0 44	3	0
30 34	0 4	0 3	1 1	0 5	9	0 9
35 39	1 °7	1 43	1 73	1 53	°5	1 6
40 44	° °	° 6	° 5	3 1	40	° 6
45-40	3 1	4 9	4 °	4		4 7
50 54	3 8	6 °	5 7	7 1	107	7 5
55 59	6 1	° 8	9 6	8	115	9
60 64	8 9	9 8	10 9	11 4	164	13 9
65 69	1° °	1° 6	13 6	17 9	163	15 9
70 79	10 5	1° 8	16 4	19 6	70 74 154	18 3
					75-79 93	16 7
80 et plus	6 ,	7 1	9	17	80 84 45	15 5
					85 & + 15	10 7
					Age Inc	—
Tous âges	° 9	3 7	3 9	4 4	1 013	4 7

N B De 1946 à 1949 il s ag t des taux calculés d après les nombres est més (vo r texte) en 1950 les ta x sont calculés d après les décès rangés sous le n° A 0 de la Nomenclature Internationale (1948)



Graphique I



Graphique II

Nous avons suppose que pour les annees anterieures a 1950 le nombre des cancers du larynx n avait pas change Nous avons donc soustrait le nombre de deces declares comme étant attribues au cancer du larynx en 1950 du total des cas declares comme cancers de l appareil respiratoire au cours des annees allant de 1946 a 1949

— Pour la *France entiere* nous avons base

(4 775 711 habitants) nous avons pu disposer des declarations de déces jusqu en *1951* mais nous n avons conserve que les deces du sexe masculin — ceux du sexe feminin etant trop peu nombreux *Tabes 1 et 2*

Les tableaux ont ete établis sexes separes ils indiquent les taux de deces pour 100 000 habitants L etude de ces tableaux donne l im pression que le nombre des decès declares comme attribues vraisemblablement au can cer broncho pulmonaire est maximum dans la tranche d age 65 69

Le *graphique I* a ete etabli pour la France entiere et le *graphique II* pour le departe ment de la Seine en prenant pour base le pourcentage d augmentation des taux de de ces d une annee a l autre dans cette tranche d age Ces graphiques revelent une augmen tation du nombre des cas supposes mais cet te augmentation se fait sans aucune regula rité

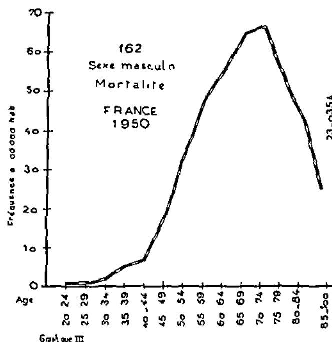
Nous ne donnons ces nombres qu a titre indicatif car les artifices que nous avons du utiliser doivent nous rendre tres circonspects dans leur interpretation

Nous avons etudie pour la France entiere et toujours pour la tranche d age 65 69 ans l importance reciproque de ces cancers chez l homme et chez la femme on constate les rapports suivants

en 1946 les cas declares de deces par can

cer, chez la femme representent 80 % de ceux de l'homme , en 1947 57 %, en 1948 36 % , en 1949 43 %, et en 1950 27 %

Il y a donc eu, en apparence, une augmentation plus rapide des cas a cet age chez l homme, l'ecart de frequence ayant crû régulierement (Le taux de deces chez la femme de 65 a 69 ans est passe de 12,2 pour 100 000 en 1946 a 15,9 en 1950, alors que celui de l homme est passe de 15,4 en 1946 a 58,6 en 1950).



Graphique III

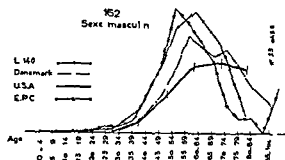
Le *graphique III* donne l aspect de la courbe de repartition des taux de deces pour le sexe masculin La gravité du pronostic du cancer du poumon permet de considerer que la morbidite et la mortalité sont pratiquement superposables , le delai moyen qui s ecoule actuellement entre les premiers symptômes reconnus et le deces se situe autour d'une année C est pourquoi on est en droit de considerer qu'une telle courbe rend compte, dans l'etat actuel de nos connaissances, de la repartition des cas selon l'âge On constate sa tendance nette a une decroissance apres avoir atteint son sommet dans la tranche d'age 65-69

* * *

Travaux parus en France depuis 1940 sur la frequence des cancers broncho pulmonaires

Un seul travail important (¹) a ete publié sur ce sujet en France pendant cette periode, malheureusement, il est base sur des series d'autopsies et comporte, de ce fait, des causes d'erreurs si grandes qu'il n'est pas possible d'en *tenir compte*

Aucune etude statistique n'a eté effectuee sur les consequences de l habitude de fumer des cigarettes Signalons que le role possible d'une atmosphere contenant une sorte d'aerosol d'huile a ete invoque pour expliquer une frequence plus grande du cancer broncho pulmonaire chez les ouvriers tourneurs (HUGUENIN, LEMOINE, FAUVET)



DISCUSSION

DR LEVIN We should record that we re

is only accidental Were the last curves shown by Dr Denoix based on frequency distributions ?

DR DENOIX I agree The last curves included figures collected for the populations of the countries concerned for each quinquennial group The numbers of cases were not totals and therefore rates were not calculated But the curves are comparable

DR CLEMMESEN I should like to congra

(¹) [illegible] fréquence des [illegible] sique [illegible] ulletin

tulate Dr Denoix on his paper I would like to make further comparisons between the Danish graphs and those of Dr Denoix and Dr Dorn

Dr Steiner A comment which applies to all prevalence studies should be put in the records They are used with value to compare one geographical area with another or in a single area to compare prevalence over different periods of years They are based on clinical diagnoses But with lung cancer accuracy of diagnosis has varied very considerably within our life time Prior to about 1920 diagnosis could only be made by physical examination and aspiration and examination of pleural fluid After 1920 diagnosis was made by X ray examination but this was at first not very accurate After 1935 bronchoscopic biopsy was also used as well as lobectomy and pneumonectomy Between 1942 to 1945 use of cytological examination of sputum and bronchoscopic washings was expanded Since 1950 there has been a tremendous development of exploratory thoracotomy All these developing methods have greatly improved clinical diagnosis

Cases still left undiagnosed are the extra pulmonic forms which the pathologist gets from the neural general and orthopaedic surgeons and the cases simulating acute chest conditions

If to morrow some new method of diagnosis emerged which was completely accurate for lung cancer then we might expect still another large increase in our incidence figures they could then not be compared with previous figures The great increase shown in clinical studies are not seen in data based on necropsies

Dr Maisin Does Dr Steiner really think that if some absolute methods of diagnosis were developed there would be much increase in the numbers of cases ? I do not think so In good centres nearly all cases are diagnosed We have so many diagnostic methods that we do not miss many cases

Dr Clemmesen I would like to support Professor Maisin We think in Denmark that [illegible]

cancer of the lung was frequently metastatic and improved diagnosis of the growth in the primary sites has probably made some difference over the years

Dr Stewart In the twenties Professor Jackson trained several men in bronchoscopy in Philadelphia It would be interesting to see what impact this had on the diagnosis of the disease in that city

Dr Maisin The proportion of lung cancer in women in France is very low compared with men Again as in Belgium outside cities the women smoke very little

Dr Levin I find it a curious type of reasoning which leads to the conclusion that improvement of diagnosis necessarily increases the number of cases occurring It might just as well lead to a decrease Yet this kind of

been followed by an increase in the incidence of cancer of the cervix

Dr Stewart I would stress the fact that there is a lot of difference between the diagnosis of cancer of the lung and cancer of the cervix One cancer of the cervix is in effect an external cancer which will ultimately lead to bleeding or discharge The other cancer of the lung is an internal cancer and the diagnosis often presents great difficulty

Dr Kuschner I would support Dr Steiner from my experience in a large general hospital Most patients unfortunately do not have available to them the services of an institute like Professor Maisin s In one special study the number of misdiagnoses was found to be 45 per cent There is undoubtedly still room for improvement in diagnosis which will lead to further increase in the number of cases

Dr De Muylder In connection with the question of improved diagnosis is it not true that in former times when clinical diagnosis was not so easy autopsy findings would have shown an increased proportion of cancer of the lung undiagnosed before death ?

Dr Kuschner *I do not know*

Dr Maisin I have been working at this institute for 29 years and I am still the same

man I find it impossible to explain the increase solely by *improved diagnosis*

DR STEWART Professor Maisin was trained in the leading cancer centres of the world before he entered practice This is not true for all medical men

DR CLEMMESEN In Copenhagen 93 per cent of all cases are treated in hospital and about 78 per cent are diagnosed by autopsy or histology and there has been a statistically significant increase while this figure remained constant When pulmonary surgery and bronchoscopy were introduced an increase due to improved diagnosis occurred for both men and women But apart from this a steady and pronounced increase can be proved beyond doubt I shall refer to my paper for details

DR LEVIN The assertion that the increase is due to improved diagnosis needs better supporting evidence, otherwise we might as well say that there are no changes in causes of mortality among the human population I think we should assume that the increase is a real one and search for possible causes for this increase If we do not think the increase is real, there is really no point in seeking causes

DR STEINER It is an historical fact that in lung-cancer an internal form of tumour-diagnostic accuracy in the living has progressed from what we might call nearly 0 per cent in 1900 to 80 per cent or more nowadays In this respect it differs from mammary skin and cervical tumours which could always be seen

DR HAMMOND I entirely agree with Dr Levin that if there has been no increase it is [illegible] increase [illegible] a satis[illegible] have been very impressed by Dr Clemmesen s studies based on the roentgen photos from the Tuberculosis Station and wonder if similar work could be extended beyond Denmark Perhaps we could hear something more about this work

DR CLEMMESEN This will form part of my paper to morrow, but perhaps I can mention a few points here In 1947 we found that death certificates — especially after 1940 — showed a marked increase in cancer of the lung We, therefore, went to our Tuberculosis Organization to see if their X-rays showed a similar increase We found that they did The marked increase in 1941 to 1942 corresponded to the introduction of routine bronchoscopy and lung surgery, (cf diagrams, pp)

DR STEINER As self appointed historian to the Symposium I would draw the attention of members to another historical fact The collective experience of the people here assembled represents many thousands of cases of cancer of the lung Yet in 1912 Adler, in his review of the subject, could find only about 250 cases in the whole of the world s literature

DR MAISIN Are not Dr Kretz' figures an answer to this question of whether the increase is real ? They are based on autopsy results (in which Dr Steiner has full confidence) and show a definite increase in Austria

DR KRETZ Our mortality data are derived about 65 per cent from autopsies and about 35 per cent from clinical findings

DR STEINER But Dr Kretz' figures only go back to 1922 and this is not far enough

DR KRETZ Real public statistics in Vienna only go back to 1930 It is no use trying to present statistics which have no basis in reality

ZUSAMMENFASSUNG

Es ist schwierig sich eine genaue Vorstellung zu machen von der Aenderung der Zahlen der Falle von [illegible] Frankreich im Zeit [illegible] Unter [illegible] welche [illegible] fschluss [illegible] geben zu kon

Die Todesbescheinigungen sind zu vielen Irrtumern unterworfen um eine solide Basis bilden zu konnen Die Verff haben seit 1946 Schatzungen aufgestellt fur ganz Frankreich und fur das Departement Seine mit der Stadt Paris (4 775 000 Einwohner) Es ist unmoglich fur die vorausgegangenen Jahre Berechnungen anzustellen denn infolge der Kriegsereignisse [illegible] Dokumente wertlos [illegible] 100 000

1950	Manner	13 1
1946	Frauen	2 9
1950	Frauen	4 7

Fur das Seine Departement hat sich die Todesrate auf 100 000 Einwohner in der folgenden Weise verändert

1946 Manner 8
1950 Manner 27 9

Die Verff glauben dass diese Zunahme der Zahlen zu einem guten Teil auf die verbesserte Diagnostik besonders in stadtischen Verhaltnissen zuruckzufuhren ist

SUMMARY

It is difficult to form an opinion on the changes in the number of cases of bronchopulmonary cancer in France from 1940 to 1950 A geographical investigation begun in 1951 is still too recent to give us information

The death certificates are influenced by too many sources of error to constitute a firm basis for conclusions We have however calculated the approximate rates for France as a whole and for the departement de la Seine including Paris with a population of 4 775 000 for the period following 1946 It is impossible to calculate reliable rates for earlier years basis data being inaccurate because of the war events

For France mortality rates per 100 000 changed as follows

1946 males 4
1950 females 13 1
1946 males 2 9
1950 females 4 7

For the département de la Seine mortality rates per 100 000 inhabitants changed as follows

1946 males 8
1950 males 27 9

It is our opinion that an important part of the increase of these figures may be due to improvements in the conditions for diagnosis in view of the higher rates for the urban region of la Seine

RESUMEN

Resulta dificil formarse una opinión de las variaciones en el numero de casos de cáncer broncopulmonar en Francia desde 1940 a 1950 Una investigación geografica comenzada en 1951 es demasiado reciente para poder ser utilizada

Los certificados de defunción estan influenciados por demasiadas fuentes de error para poder constituir una base solida de conclusiones Sin embargo hemos calculado las cifras aproximadas para toda Francia y para el departamento del Sena incluido Paris con una poblacion de 4 775 000 y durante el periodo después del año 1946 Es imposible calcular cifras de garantia para años anteriores ya que los datos básicos son inexactos por culpa de los acontecimientos de la guerra

En Francia las cifras de mortalidad por 100 000 variaron como sigue

1946 varones 4
1950 hembras 13 1
1946 varones 2,9
1950 hembras 4 7

En el departamento del Sena las cifras de mortalidad por 100 000 habitantes variaron como sigue

1946 varones 8
1950 varones 27 9

En nuestra opinion una parte importante del aumento de estas cifras se deberia al mejoramiento de los medios diagnosticos si se tienen en cuenta las cifras mas elevadas en la region urbana del Sena

RESUME

Il est difficile de se faire une idée de l'évolution du nombre de cas de cancer broncho pulmonaire en France de 1940 à 1950 Une enquête geographique avant débute en 1951 est trop recente pour pouvoir fournir des renseignements

Les déclarations de deces sont sujettes a de trop nombreuses causes d'erreurs pour fournir une base solide Nous avons établi des taux approximatifs pour la France et pour le departement de la Seine englobant Paris (4 775 000 habitants) depuis 1946 Il est impossible de calculer des taux valables pour les années antérieures car du fait de la guerre les documents de base sont sans valeur

Pour la France le taux de deces pour 100 000 habitants a évolué de la façon suivante

1946 sexe masculin 4
1950 sexe masculin 13 1
1946 sexe feminin 2 9
1950 sexe feminin 4 7

Pour la Seine le taux de deces pour 100 000 habitants a évolue de la façon suivante

1946 sexe masculin 8
1950 sexe masculin 27 9

Nous pensons qu'une part importante de l'augmentation de ces nombres est due a l'amélioration des conditions du diagnostic témoin le taux plus élevé dans une region urbaine (Seine)

RIASSUNTO

E difficile di avere un'idea dell evoluzione del numero dei casi di cancro broncopolmonare in Francia dal 1940 al 1950 Una ricerca statistica e stata iniziata nel 1951 ma è troppo presto per fornire qualche informazione

Le denuncu di morte sono soggette a cosi frequenti cause di errore perche possano rappresentare una solida base valutativa Noi abbiamo stabilito delle percentuali approssimative per la Francia e per il Dipartimento della Senna compresa Parigi (4 775 000 abitanti) per il 1946 Risulta impossibile valutare le percentuali negli anni precedenti perchè le vicende belliche hanno privato di qualsiasi valore ai documenti di accertamento Per la Francia le percentuali di decessi per 100 000 abitanti ha avuto la seguente variazione

1946 sesso maschile 4 — sesso femminile 2 9
1950 sesso maschile 13 1 — sesso femminile 4 7

Per la Senna la percentuale di decessi su 100 000 abitanti ha variato nel modo seguente

1946 sesso maschile 8
1950 sesso maschile 27 9

Si ritiene che un fattore importante nell aumento di queste cifre e dovuto al progresso dei mezzi diagnostici come e documentato dalla percentuale piu elevata nei centri urbani

SOME STATISTICAL INFORMATION ON CANCER OF THE LUNG IN THE NETHERLANDS

BY

M G NEURDENBURG
(Staatstoezicht op de Volksgezondheid Amsterdam Holland)

INTRODUCTION

Administration of hospitals in Amsterdam

About 80 per cent of all cases of in door hospitalization in Amsterdam and of inhabitants of Amsterdam hospitalized elsewhere are administrated by the Municipal Public Health Service i e all admissions into the Municipal and University Hospitals and the main portion of those into the private hospitals are controlled by the Admission Division of that service This system has been in force already since the end of World War I and practically applies to all patients under Poor Law and insurance schemes in all hospitals and also to the small number of private patients in the Municipal and University hospitals

Before 1941 there was in practice a rather liberal tariff of municipal subvention in case of hospitalization which tariff was under the still existing Poor Law regulations The main difference from that period is that now the major part of the costs of this way of hospitalization are paid under contract by the Sickness Funds and not any longer under the Poor Law

Since at the end of 1941 a still temporary scheme came into force the control of the P H Service has been continued as by agreement the Sickness Funds are making use nowadays of the already existing machinery *The groups under this insurance scheme have augmented in some respects but the pro*

not precisely
he population
before 1941

will be under this scheme nowadays and is therefore included in the data of these hospital statistics

[illegible]

pitalization are *not* under this administration

Therefore it may be estimated that these hospital statistics cover about 80 per cent of all days of hospitalization in Amsterdam

No cases under these schemes are admitted into the hospitals without consent of the Municipal P H Service which is responsible for the distribution of beds for these patients *(Out door patients are not included in these statistics)*

The fact that the administration has altered only slightly since pre war times allows comparisons with data of 1935 which I published in a special cancer number of the « Tijdschrift voor Sociale Geneeskunde » in November 1936

These statistics are collected per case repeated admissions and transfers to other hospitals (not to other wards in the same hos

[illegible] cases The ca

The statistical data are collected from punch-cards prepared by *the foresaid medico* statistical divis on which I have been serving from 1926 till June 1951 so I may say that I have been responsible for the contents of same data which I may use for this paper with the courtesy of the reponsible director

A fuller description of this statistical administration and its details may be found in older publications and reports

Registration of cancer in the Netherlands

The organization for the registration of cases of cancer in the Netherlands will start in the end of 1952 in two pilot d str cts of about one million inhabitants each Our general system of vital statistics on number of inhabitants deaths age distribution etc will allow comparison between municipalities and

districts and this unique position gives us an opportunity for direct comparison of the numbers of cases registered in the hospitals with the numbers of residents in each municipality etc We shall start with data collected from hospitals because as a rule the major part of patients will pass through a hospital at least once during their illness from cancer Gaps will be covered later by other measures With regard to cancer of the lung this procedure will be sufficient for the nearest future

TABLE I

Hospital statistics Amsterdam (Neths) (± 80 per cent of ± 840 000 inhabitants)		Persons discharged during 1950						Machine-code A dam
		MALES		FEMALES		Whereof deaths		
Int. Stat Classif W H O 1948	Malignant neoplasm of (num. indicated by + are parts of a total)	Num cases	Days	Num cases	Days	M	F	
140 148	Mouth and pharynx	12	518	5	165	3	1	3200
150	Oesophagus	35	1388	12	508	8	4	3210
151 152+	Stomach, duodenum	134	5163	94	3571	54	41	3220
152+ 153	Intestines (excl duod)	55	2258	58	3176	2[illegible]	30	3230
154	Rectum	57	3524	45	2975	12	16	3240
155 156	Liver biliducts	16	424	27	1455	7	21	3250
157	Pancreas	12	463	11	457	10	9	3260
158 159	Peritoneum other dig	7	373	12	460	3	5	3270
160 161	Nose, sinuses larynx	16	579	4	121	3	1	3280
162 165	Trachea lung, mediast	165	6681	25	1400	59	8	3290
170	Breast	3	38	150	6030	—	39	3300
171	Cervix uteri	—	—	76	2958	—	13	3310
172	Corpus uteri	—	—	52	2032	—	6	3311
173	Uterus (other parts)	—	—	16	399	—	—	3312
174	Uterus NOS	—	—	37	1167	—	8	3313
175	Ovary, tuba, lig latum	—	—	58	3160	—	20	3314
176	Other and NOS fem gen	—	—	30	1214	—	4	3315
177	Prostate	86	4600	—	—	21	—	3320
178	Testis	8	168	—	—	—	—	3321
179	Other and NOS male g	9	579	—	—	1	—	3322
180	Kidney, ureter	18	1021	8	266	7	3	3323
181	Bladder, other urinary	18	1311	17	957	5	7	3324
190	Melanoma cutis	—	—	2	37	—	1	3330
191	Skin (others)	6	226	9	509	3	3	3331
192	Eye	3	91	6	111	—	—	3340
193	Brain other nervous s	19	455	13	797	13	8	3350
194	Thyreoid gland	3	86	6	469	1	2	3360
195+	Adrenal gland	—	—	2	127	—	2	3370
195+	Other endocrine glands	2	18	1	48	2	—	3390
196	Bone	11	460	13	518	—	6	3380
197	Connective tissue	6	215	3	239	—	1	3381
198	Lymphnodes (second, etc)	5	171	3	62	[illegible]	—	3400
199	Other and NOS sites	17	642	23	2348	5	6	3399
200	Lympho reticulosarc	7	294	14	769	3	8	3410
201	Hodgkin s disease	20	1605	15	1312	8	5	3420
202	Lymphoma (other forms)	11	537	6	128	1	2	3430
203	Multiple myeloma	4	582	1	19	1	1	3440
204	Leucaemias aleucaemias	23	748	28	1302	15	14	3450
205	Mycosis fungoides	—	—	—	—	—	—	3460
Totals		788	35218	882	41266	274	295	

Dr M G Neurdenburg (July 1952) = Source unpublished data collected by the Municipal Central Bureau of Public Health

The basis of this registiation has been financed by a grant-in-aid of the Queen Wilhelmina Fund, a large institution which is the result of a gift from the Dutch population to their beloved Queen at her abdication

The recommendations of the W H O (techn Rep Ser 53) will be followed in the building up of our system of registration in order to ensure international comparability

The Central Committee on Cancer Problems is the technical adviser of the Queen Wilhelmina Fund and has recommended centres of canceiology to be created in each university and in both cancer institutes in Amsterdam and Rotterdam Follow-up of cases will be organized with the help of the well-known private agencies called the « cross-societies » which participate in so much medical and social wellfare work like home nursing, consultation centres etc The registry will stimulate this follow-up system by questionnaires at well timed intervals

Under the auspices of the Queen Wilhelmina Fund and the Central Committee on Cancer Problems a team consisting of a geologist and a medical man studies the differences in rates of mortality in recent years for each municipality and district, since it has been supposed that differences in e g soil and/or water supply have some relation to differences in mortality from cancer In close cooperation with the Netherlands' Central Bureau of Statistics all detailed data on mortality from cancer will be deposited in a special archive and made available to all research workers

Nomenclature used

Before 1950 a modification of the Bertillon List have been in use by the municipal P H service, which in 1950 has been adapted to the International Statistical Classification of Diseases etc (W H O 1948) Some categories of minor interest have been joined however, as these hospital-statistics in the first place are serving administrative purposes of the municipality and the insurance scheme But the difficulties arising from these modifica-

have been taken in former times as now-

Unfortunately it was not possible to differentiate between the num 162-165 of the 1948-list but the number of cases included in this group of sites other than the lung itself will be very small

The details of the older list were not given to the same extent but they allow a comparison with 1935 rather well (see table 3)

Table 1 Of 788 cases of malignant neoplasms of men there were 165 of the lung c a (20 9 %) and of 882 of women 25 only (2 8 %

of thi

other

The same is seen with regard to the duration of hospitalization 6681 days of a total of 35218 for men (19,0 %) and 1400 days of a total of 41266 for women (3 4 %)

The death-rate, in as far as it would be allowed to calculate such a rate, is 35,8 % for men and 32 0 % for women

Malignant neoplasms of the respiratory sites are one of the major parts of the total experience of hospitalization

Malignant neoplasms of the female breast are outlined in number of cases and of days by the neoplasms of the lung c a of men by ± 10 per cent. Another comparison might be given by the number of cases of malignant neoplasms of the uterus, 181 cases with 6556 days

The malignant neoplasms of the stomach and duodenum are less in number among men (134 cases with 5163 days) but nearly 4 times the number of lung cases among women (94 cases with 3571 days)

The age-distribution of all sites and of the respiratory sites are compared in *table 2*

The age group of 60 to 79 years is responsible for about 50 per cent of all cases and days with men as for all sites as for lung-cancer For women these proportions are less

vely large number of hospitals The adaption of 1950 was directed by the wishes of keeping in line with historical nomenclature and of serving international comparability Pains

the same lines as may be seen in other parts of the world There are several changes in diagnostic procedures and in therapeutic possibilities There may be some alterations in

TABLE II

Hospital statistics Amsterdam (Neths) : (± 80 per cent of ± 840 000 inhabitants)
Persons discharged during 1950

Age groups	MALES All sites num 140-205 cases	days	MALES Whereof num 162 165 cases	days	FEMALES All sites num. 140 205 cases	days	FEMALES Whereof num. 162 165 cases	days
0	1	12	—	—	1	42	—	—
1 4	4	132	—	—	7	173	—	—
5 14	10	442	—	—	2	88	—	—
15 19	4	144	—	—	4	157	—	—
20 29	16	870	1	49	17	848	—	—
30 39	32	2482	—	—	68	3812	3	108
40 49	71	2631	22	888	146	6863	5	452
50 59	213	8554	66	2431	236	9811	6	360
60 79	397	18353	76	3313	368	17762	11	480
80 +	40	1598	—	—	33	1710	—	—
Totals	788	35218	165	6681	882	41266	25	1400
Idem, but deaths only :								
0	1	12	—	—	1	42	—	—
1 4	—	—	—	—	—	—	—	—
5 14	4	133	—	—	1	80	—	—
15 19	2	77	—	—	—	—	—	—
20 29	2	10	—	—	5	427	—	—
30 39	9	1140	—	—	20	2205	—	—
40 49	24	1052	9	439	45	2199	2	94
50 59	71	2367	21	733	65	3109	—	—
60 79	146	6466	29	1419	145	7254	6	340
80 +	15	687	—	—	13	923	—	—
Totals	274	11924	59	2591	295	16239	8	434

Source unpublished data collected by the Municipal Central Bureau of Public Health = Dr M G Neurdenburg (July 1952)

the Amsterdam hospitalization policy due to other factors than mentioned above

It is a pity that the respiratory group was a part only of a much larger group in 1935, which hampers the comparisons , but keeping in mind the composition of group K, one may be impressed, however, by the heavy toll of the respiratory sites This is accentuated, if one considers the much smaller changes in other groups such as A, B, C, and E

May I draw the attention to groups D (rectum), H (male genital organs, of which the prostate is the biggest part), F (female genital organs), and G (female breast) Part of the changes in these groups may be explained by improvements in diagnosis and therapy, but does the same hold for lung-cancer, too ?

The difficulty of *table 3* is that neoplasms of respiratory sites are not the only « newer » sites, which are included in group K (i a brains)

Table 4 shows the number of deaths from malignant neoplasms among the general population and in the hospital statistics for the two years 1935 and 1950 as a continuation of table 3

Table 5 gives the numbers of deaths among the ge[…]lation of Amsterdam, the ca-

TABLE III

Hospital statistics Amsterdam (Neths)	CASES						DAYS		DEATHS	
	Males		Females		Persons		Persons		Persons	
	1935	1950	1935	1950	1935	1950	1935	1950	1935	1950
A 140 148, 196[a]	19	12	9	5	28	17	763	683	5	4
B 150	28	35	6	12	34	47	807	1896	21	12
C 151, 152[b]		134		94		228		8734		95
155, 156		16		27		43		1879		28
Total C	157	150	111	121	268	271	11220	10613	151	123
D 154	37	57	27	45	64	102	3883	6499	25	28
E 152[c], 153		55		58		113		5434		57
157		12		11		23		920		19
158, 159, 198[d], 199[e]		7		12		19		833		8
Total E	75	74	77	81	152	155	8125	7187	76	84
F 171 176	—	—	185	269	185	269	8491	10930	45	51
G 170	3	3	122	150	125	153	5862	6068	35	39
H 177 179	58	103	—	—	58	103	3007	5347	25	22
I 190, 191	6	6	5	11	11	17	354	772	4	7
K 160, 161		16		4		20		700		4
162 165		165		25		190		8081		67
180, 181		36		25		61		3555		22
192 200[f], 202, 203		88		91		179		9186		64
Total K	89	305	52	145	141	450	6618	21522	79	157
TOTALS	472	745	594	839	1066	1584	49130	71517	466	527
Whereof MALES	472	745	—	—	472	745	19740	32865		251
FEMALES	—	—	594	839	594	839	29390	38652		276
— 201 (1950 only)		20		15		35		2917		13
— 204 (idem)		23		28		51		2050		29
— 205 ((idem)		—		—		—		—		—
GRAND TOTALS 1950		788		882		1670		76484		569

Notes (in or exclusions 1950 and/or 1935)

a 1935 incl bones of jaws
b 1935, 1950 duodenum
c 1935 1950 excl duodenum
d 1935 incl abdominal lymphnodes
e 1935 incl abdominal NOS
f 1935 excl a (bones of jaws), d (abdom lymphnodes), e (abdominal NOS)
g 1935 1950 excl Hodgkin leucaemias and aleucaemias mycosis fungoid

Malignant neoplasms of
A Mouth and pharynx
B Oesophagus
C Stomach, duodenum, liver, bileducts
D Rectum
E Intestines (excl duodenum), pancreas peritoneum, other digestive org
F Female genital organs (excl breast)
G Breast (male and female)
H Male genital organs
I Skin
K Nose larynx, trachea bronchus lung mediastinum thorax urinary system eye brain nervous system, *endocrine glands bone connective* tissues, malignant lymphomata, etc

Dr M G Neurdenburg (July 1952)

Sources 1935 «Kanker en Ziekenhuisverpleging» (Cancer and Hospitalization) in Tijdschr v Soc. Geneeskunde, Nov 1936, p 229 seq
1950 unpublished data collected by the Municipal Central Bureau of Public Health

TABLE IV

M = males, F = females, P = persons (M + F)		A	B	C	D	E	F	G	H	I	K	Total
		Malignant Neoplasms of (Legend vide Table III)										
General population Total deaths	1950 M	15	26	195	28	77	—	—	59	5	247	679
	F	5	11	168	29	95	119	142	—	6	108	712
	P	20	37	263	57	172	119	142	50	11	355	1391
	1935 P	24	52	418	75	124	112	98	49	5	157	1114
Hospital statistics Deaths	1950 P	4	12	123	28	84	51	39	22	7	157	527
Whereof	M	3	8	61	12	40	—	—	22	3	102	251
	F	1	4	62	16	44	51	39	—	4	55	276
Deaths	1935 P	5	21	151	25	76	45	35	25	4	79	466
Cases (total)	1950 P	17	47	271	102	155	269	153	103	17	450	1584
	1935 P	29	34	268	64	152	185	125	58	11	141	1066
Whereof Males	1950	12	35	150	57	74	—	3	103	6	305	745
	1935	19	28	157	37	75	—	3	58	6	80	472
Females	1950	5	12	121	45	81	269	150	—	11	145	839
	1935	9	6	111	27	77	185	122	—	5	52	594

Source Deaths Amsterdam Municipal Bureau of Statistics (unpubl.)

TABLE V

D = deaths among general population Amsterdam (residents)
c = cases, d = deaths in hospital-statistics

Ages	Inhab 1-1-50	All sites D	All sites c	All sites d	Deaths (162-165) 162	163	164	165	tot	162-165 c	162-165 d	Per 100 000 inhab All sites D	All sites c	162-165 D	162-165 c
MALES															
-0	7991	1	1	1	—	—	—	—	—	—	—	12	12	—	—
1-4	35433	1	4	—	—	—	—	—	—	—	—	3	11	—	—
5-14	58773	1	10	4	—	—	—	—	—	—	—	2	17	—	—
15-19	28094	2	4	2	—	—	—	—	—	—	—	7	14	—	—
20-29	66600	8	16	2	—	—	—	—	—	1	—	12	24	—	1
30-39	59649	15	32	9	—	—	—	—	—	—	—	25	54	—	—
40-49	54874	41	71	24	7	13	1	—	21	22	9	75	129	38	40
50-59	47373	144	213	71	19	29	1	1	50	66	21	304	450	106	139
60-79	44206	396	397	146	14	67	2	—	83	76	29	896	898	188	172
80 +	2820	70	40	15	—	3	—	—	3	—	—	2482	1418	106	—
Total	405813	679	788	274	40	112	4	1	157	165	59	167	194	37	41
FEMALES															
-0	7618	1	1	1	—	—	—	—	—	—	—	13	13	—	—
1-4	33769	—	7	—	—	—	—	—	—	—	—	—	21	—	—
5-14	56191	1	2	1	—	—	—	—	—	—	—	2	4	—	—
15-19	27233	—	4	—	—	—	—	—	—	—	—	—	18	—	—
20-29	70113	9	17	5	—	—	—	—	—	—	—	13	24	—	—
30-39	65552	21	68	20	—	—	—	—	—	3	—	32	104	—	5
40-49	61461	86	146	45	1	2	—	—	3	5	2	140	238	5	8
50-59	52300	143	236	65	—	2	1	—	3	6	—	273	451	6	11
60-79	51071	368	368	145	2	7	—	—	9	11	6	721	721	18	22
80 +	4713	83	33	13	—	3	1	—	4	—	—	1761	700	85	—
Total	430021	712	882	295	3	14	2	—	19	25	8	166	205	4	6

TABLE VI

MORTALITY *from* MALIGNANT NEOPLASMS *of trachea, bronchus and lung (*)*
per 100 000 inhabitants of each age group in the Netherlands (N) and in France (F) 1946 1951

Ages	MALES						FEMALES					
	1946	1947	1948	1949	1950	1951	1946	1947	1948	1949	1950	1951
0 — N	—	0,2	—	0,2	—	0,3	0,2	—	0,2	0,2	0,2	0,3
— 4 F	0,1	0,3	0,1	0,1	0,1		0,1	—	0,1	0,1	0,1	
5 — N	—	—	—	0,2	—	—	—	0,2	0,2	—	—	—
— 9 F	—	0,2	0,2	0,2	0,3		0,2	0,1	—	—	—	
10 — N	0,2	—	—	—	—	0,5	—	—	—	—	—	—
— 14 F	0,1	—	—	0,1	0,1		0,1	0,1	0,2	—	0,1	
15 — N	0,5	0,2	—	0,2	—	—	—	0,5	—	0,3	—	—
— 19 F	0,3	0,5	0,4	0,3	0,3		0,4	0,2	0,1	0,5	0,1	
20 — N	0,5	—	0,2	0,2	—	—	0,5	1,0	0,5	0,3	—	0,3
— 24 F	0,3	0,3	0,7	0,3	0,4		0,4	0,5	0,3	0,1	0,1	
25 — N	0,8	0,5	1,3	—	0,5	0,5	—	—	—	0 3	0,5	0,5
— 29 F	0,6	1,1	0,9	1,2	0,6		0,6	0,7	0,4	0,4	0,2	
30 — N	2,0	1,2	0,3	1,8	1,5	1,7	0,3	1,1	1,4	0,3	—	0,8
— 34 F	0,7	0,7	1,0	0,5	1,3		0,4	0,3	1,1	0,5	0,9	
35 — N	4,9	3,7	6,1	6,0	3,6	7,4	0,9	1,2	1,2	1,7	1,4	1,1
— 39 F	2,2	1,8	2,7	1,7	2,1		1,2	1,4	1,7	1,5	1,6	
40 — N	12 3	13,8	13,9	17,2	16,4	15,4	2,7	2,5	3,7	2,7	2,4	2,4
— 44 F	6,8	7,0	6,0	6,7	5,9		2 2	2,6	2,5	3 1	2,6	
45 — N	22,8	28,7	28,1	31,6	30,1	34,6	5,7	4,2	3,8	4,7	4,9	3 5
— 49 F	8,7	15,5	17,9	12,9	15,9		3,1	4 9	4,2	4,7	4,7	
50 — N	51,3	57,6	58,2	62,5	65,8	66,7	8,6	5,1	5 8	6,5	3,0	6,6
— 54 F	6 9	10 5	20,3	31,5	30,6		3 8	6,2	5,7	7,1	7,5	
55 — N	62 2	60,2	85,7	80,7	93,7	111,6	8,6	7,5	9,2	10,7	6,1	11,8
— 59 F	10,0	18,1	21,6	27,5	43,5		6,1	9,8	8,6	8,0	9,0	
60 — N	73,7	87,4	105,7	101,8	121,1	123,4	9,6	12,7	11,9	8,4	13,5	13,7
— 64 F	13,9	23,1	28,4	36,3	50,5		8,9	9,8	10,9	11,4	13,9	
65 — N	75,4	108,3	107,9	132 4	107,6	146,5	14,7	18,9	15,9	23,4	17,8	22,3
— 69 F	15,4	21,7	36,9	39,7	58,6		12,2	12 6	13,6	17,9	15,9	
70 — N	80,8	73,2	113,5	132,5	139,0	145,0	12,2	25 3	20,2	30,0	23,4	27,7
— 74 F					59,4						18,3	
75 — N	80,5	70,5	124,5	109,5	119,7	111,5	30 9	44,6	31,2	35,4	23,6	31,5
— 79 F					47,0						16,7	
70 — N												
— 79 F	15,7	32 8	32,9	43 2			10,5	12,8	16,4	19,6		
80 — N					79,5	124,2					18,3	17,7
— 84 F					42,5						15 5	
85 + N					58,0	76,6					40,5	27,5
F					22,0						10,7	
80 + N	42 5	20 0	80,0	78,7			11,0	20,1	35,1	22 4		
F	5 4	8 8	2,2	27,8			6,5	7,1	9,3	17,0		
All N	15,7	17,2	21,3	22,7	23 4	26,6	3,0	3 8	3,7	4 0	3,3	4,1
ages F	4,0	6 6	11,9	9 8	13,1		2 9	3,7	3,9	4,4	4,7	

(*) Netherlands 1946 '49 no 47b of the Int List of Causes of Death (1938)
1950 51 no A50 of the Intermediate List (WHO — 1948)
France 1946 '49 estimates (vide Dr Denoix s report)
1950 no A50 of the Intermediate List (WHO — 1948)
Comparative table prepared by Dr M G Neurdenburg (Amsterdam)
Sources Data by courtesy of the Neths Central Bureau of Statistics and from a report of Dr Denoix (France) for the Louvain — Symposium

pital, together with cases and deaths from cancer of the lung, trachea, and mediastinum by sex and age in quinquennial periods It appears that the picture for the capital corresponds to the picture from *table 6* although at a still higher level with 188 deaths from cancer of the lung, trachea, and mediastinum in the age class of 60 to 79 years

In *table 6* and *figure 5* the Netherlands figures for the mortality for malignant neoplasm of lung, bronchi, and trachea given by age and sex have been compared with the figures for France quoted from Dr Denoix On the whole the Dutch figures for men amounts to twice the French ones and it will be a matter of further research to explain these serious differences of which no analogy is found for women For women the Dutch figures are more equal to the French ones although these in some places exceed the figures for the Netherlands However, a number of more than 145 deaths per 100 000 males of 65 to 69 and of 70 to 74 years of age for 1951 is not very reassuring

Due to slight alterations and the lack of closer specification of diagnoses it is impossible to make out more details for lung cancer alone It would seem to me that one should not overlook the fact that cancer of the lung is a « new » disease Twentyfive years ago when I entered the statistical division of the Public Health Service of Amsterdam one of my seniors rather sarcastically welcomed me as the young man who would have to prove that even in medicine statistics might be of some use, for instance in order to solve the problem why some cases of cancer of the lung occurred After 25 years I left that job even without the result of having solved this problem, not withstanding that many more cases occur nowadays

I give our data without much comment as a contribution of factual figures for the purpose of research

It is an open question whether the endemiology or perhaps the epidemiology of cancer with all its complicated phenomenons will ever reveal its genotypus or not, but in spite of the relative frequency of the disease its

As a representative of the Netherlands' Cancer Research I express the hope to learn more than I will be able to procure myself from my own country

ZUSAMMENFASSUNG

Der Verf gibt einen Ueberblick uber die Administration der in Amsterdam hospitalisierten Falle und uber die Registrierungsorganisation der Krebssterblichkeit und der Karzinome der verschiedenen Organe *in den Spitalern von Amsterdam wahrend des Jahres* 1950 und es wird ein Vergleich mit dem Jahre 1935 angestellt Es wird ebenso eine Darstellung gebracht uber die Mortalitat der Karzinome der Lunge, der Trachea und der Bronchien in Amsterdam im besonderen und in den Niederlanden im allgemeinen fur die verschiedenen Altersklassen Diese Ergebnisse werden mit den entsprechenden aus Frankreich verglichen

SUMMARY

The author gives a survey of the administration of hospital cases in Amsterdam and of the organization of the registration of deaths of cancer in the Netherlands Furthermore tables with figures are given on the number of cases of cancer of various sites in the hospitals of Amsterdam during 1950 and a comparison is made of figures from 1935 and from 1950 Mortality figures are also given for deaths from cancer of lung, trachea, and bronchi in Amsterdam and in the Netherlands as a whole distributed according to age and these figures are compared with corresponding figures from France

RESUMEN

El autor hace una exposicion de la administracion de casos hospitalarios en Amsterdam y de la organización del registro de fallecimientos por cancer y numero de casos de cancer de varios órganos en los hospitales de Amsterdam durante 1950 y hace una comparacion de las cifras de 1935 y 1950 Se exponen tambien las cifras de mortalidad de los fallecimientos por cáncer de pulmon de traque y bronquios en *Amsterdam y en todos los Paises Bajos, distribuidas* segun la edad y estas cifras son comparadas con las correspondientes de Francia

RESUME

L Auteur fait un exposé des cas hospitalisés a Amsterdam et décrit l enregistrement de la mortalite due au cancer L Auteur cite le nombre de cas de cancer rencontres a l hôpital d Amsterdam pour chaque région anatomique ceci pour l année 1950 Il compare les resultats avec ceux datant de 1935 et 1950

L'Auteur presente également les chiffres exprimant

pour Amsterdam et pour les Pays Bas en général, la mortalité due au cancer du poumon, de la trachée et des bronches Les données sont classées suivant l'âge, et comparées à des données correspondantes émanant de France

RIASSUNTO

L'A passa in rassegna i casi ricoverati negli ospedali di Amsterdam e riferisce sulle denuncie di morte per cancro, in rapporto alle varie localizzazioni, durante il 1950, raffrontandole con quelle del 1935 e del 1950 Inoltre presenta le percentuali di mortalità per cancro del polmone, della trachea e dei bronchi che si sono avute in Amsterdam e nei Paesi Bassi I dati riferiti sono classificati secondo l'età e paragonati a quelli corrispondenti alla popolazione francese

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés

Nous le regrettons et nous en excusons vivement

La Rédaction

ON CANCER OF THE LUNG IN THE NETHERLANDS

BY

R KORTEWEG

(Amsterdam The Netherlands)

According to the mortality statistics from 1924 to 19o0 lung cancer mortality in the Netherlands showed a great increase espe cially in males *(Table 1)* About 1924 the ratio of lung cancer mortality between males and females was 2 1/2 1 about 19o0 it was 6 1

In 1945 the last year of the war and in

TABLE I

Mortal ty from cancer all s tes and from lung cancer by sex in the Netherlands 1924 1951 (Centr Bur v d Stat st ek)

Year	Estimated population (Thousands) *	Deaths from cancer all sites		Deaths from lung cancer **			
		Males	Females	Males		Females	
19 4	7 °64	893	4 °40	58	1 6	°3	0 6
19°5	7,36	3 939	4 404	7°	° 0	°9	0 8
19°6	7 469	4 036	4 603	84	2 °	38	1 0
19°7	7 571	4,3 9	4 89	108	° 9	5	1 4
19°8	6 4	4 361	4 808	140	3 7	5	1 4
19°9	7 6	4 473	4 997	15°	4 1	61	1 6
1930	880	4 70°	4 963	187	4 7	0	1 8
1931	7 999	4 741	5 16°	°07	5 2	77	1 9
193°	8 1 °	4 7°6	5 216	°40	5,9	69	1 7
1933	8 °37	4 8 9	5 4 5	277	6 7	74	1 8
1934	8 341	4 889	5 49o	°79	6 7	85	° 0
1935	8 433	5 000	5 641	332	7 9	106	° 5
1936	8 516	5 °96	5 8o4	368	8 6	1°4	° 9
1937	8,59°	5 3°9	5 943	433	10 1	1 5	° 9
1938	8 684	5 6°8	6 170	475	10 9	11o	2 6
1939	8 7°1	5 641	6 087	493	11 °	130	3 0
1940	8 ° 8	5 889	6 377	534	1° 0	1°	° 9
1941	8 965	6 5°6	6 ° 0	648	14 0	146	3 3
1942	9 042	6 349	6 71	69	15 °	190	4 °
1943	9 10	6 °10	6 843	30	16 0	151	3 3
1944	° 174	6 490	6 7°3	°98	15 °	16°	3 6
1945	9 26°	o 64	6 513	576	1 4	153	3 3
1946	9 4 3	o 75°	6 35	739	15 7	14°	3 0
1947	9 6 9	6 5°	6 489	8°°	17 °	183	3 8
1948	9 800	6 664	6 716	1 038	°1,2	180	3 7
1949	9 956	6 966	7 031	1 1°5	°° 6	°00	4 0
1950	10 114	54	31°	1 °15	°4 0	1 9	3 5
19o1	10 °64	7 746	7 5 9	1 359	°7 1	230	4 5

* M d year total popu at on F gu es given to neare t thou and

** Lung cancer Cancer of lung pleu a bronchus and me l a t num (In 1950 and 1951 Group 16° 163 and 164 of the new nternat onal clas f cat on)

1946 and 1947 the number of cancer deaths recorded in the Netherlands showed a sudden, though only temporary, decrease. For females this amounted to 6 per cent and for males to 9 per cent. In lung cancer the decrease was most pronounced in 1945, in gastric cancer in 1946 In several other cancers, e g. breast cancer, there was no decrease at all. In this respect each cancer, therefore, must be considered separately.

The cause of this temporary decrease is not clear. It may have been due to under-nourishment or to metabolic and hormonal disturbances of the population, or to the deterioration of diagnostic facilities, e.g. the impossibility of taking Roentgenograms Finally there is a possibility that the decrease in lung cancer may have been caused by lack of tobacco.

In 1951, in the Binnengasthuis in Amsterdam, a general hospital without a department for thoracic surgery, 22 per cent of all cancers in males proved at autopsy to be lung cancer (3 per cent in females); in the combined hospitals of Rotterdam this percentage amounted to 29 (4 in females)

A mass-screening for tuberculosis in Amsterdam, in 1951 and 1952, revealed a malignant lung tumour in one out of every 4800 persons over 14 years of age, males and females together. In the industrial town of Schiedam and surroundings this figure was one out of every 7000 persons, of all ages, males and females together In both investigations the material was practically unselected

The mortality figures of to-day do not give an accurate impression of the extension of the risk of lung cancer which is threatening (1). From the shape of the age curve for lung cancer, with its great deficit in mortality for the higher age groups, it may be assumed with considerable certainty that in the Netherlands and in England mortality from lung cancer will before long amount to 25 to 40 per cent of the total mortality from cancer of all sites in males (2) This increase in lung cancer mortality will cause a sharp rise in the total cancer mortality in males In England this rise has already begun (3).

From *Table II* it appears that the habit of cigar smoking is diminishing rapidly, whereas cigarette smoking has become very popular of late years. A great proportion of cut tobacco is smoked in the form of self-made cigarettes In the Netherlands females began smoking about the end of the first world war

TABLE II

*Tobacco products for inland consumption per head of the total population of the Netherlands, for the years 1923-1951, according to data of the tobacco-tax-revenue ****

Year	Cigars (number)	Cigarettes (number)	Cut tobacco ** (per kg)
1923	146	274	1,8
1924	143	346	2,0
1925	144	269	1,4
1926	153	317	1,7
1927	158	342	1,6
1928	165	364	1,5
1929	173	409	1,4
1930	174	456	1,5
1931	171	444	1,5
1932	167	450	1,6
1933	171	475	1,5
1934	171	471	1,3
1935	169	475	1,2
1936	171	466	1,3
1937	174	506	1,2
1938	178	549	1,2
1939	191	596	1,3
	unreliable on account of war		
1946	84	354	0,5
1947	94	557	0,8
1948	90	545	0,9
1949	93	616	1,1
1950	78	793	1,2
1951	70	822	1,0

** Smoking and chewing tobacco and shag
*** By courtesy of the Netherlands Centraal Bureau voor de Statistiek, the Hague

In *Table III* tobacco consumption per adult (i e aged 15 and over) per annum for the years 1939 and 1949 is given for a number of countries During the war and the first years after the war tobacco consumption was very low in the Netherlands, whereas in the last few years it has rapidly been increasing again

Table IV gives the mid-year total population by age for the Netherlands and for England and Wales, over a number of years. This table is given as a warning that, in comparing two countries, due account should be

TABLE III

Tobacco consumption per adult (i e aged 15 and over) per annum (The Journal of the Royal Statistical Society Series A general Vol 113, Part 4, 1950, p 504)

Country	Cigarettes (pieces)		All tobacco products (grammes)	
	1939	1949	1939	1949
Australia	615	909	1996	2586
Belgium	1035	1228	3855	2903
Canada	856	1772	2359	3311
Denmark	612	894	3447	2722
France	589	858	1678	2087
Irish Republic	1413	2308	2177	2048
Italy	671	861	1089	1134
Netherlands	828	857	4173	3519
New Zealand	709	1294	2631	4082
Norway	361	980	1588	2404
South Africa	663	1038	1588	1860
Spain	490	484	1588	1452
Sweden	402	710	1633	1860
Switzerland	733	1251	2495	2958
U S A	1750	3189	3856	4581
Great Britain	1955	2029	2495	2495

taken of the age construction of the populations concerned

*
* *

According to all those who have investigated this matter, a high correlation exists between heavy smoking and lung cancer

Up till now, nobody has succeeded in making it plausible that lung cancer could be caused by the prolonged action of so called carcinogenic substances in tobacco smoke (4, 5) However, our knowledge of cancer enables us to understand that even tobacco smoke without carcinogenic potentialities might promote the arising of lung cancer (2, 6) There are several possibilities :

Tobacco smoke might prepare the bronchial mucosa for the action of carcinogens of other origin

After « latent » tumour cells have been formed by the action of a carcinogen of other origin, tobacco smoke might act as a « promoter » in the sense Peyton Rous gave to this word and provoke these latent tumour cells to grow to actual clinical cancers (7, 8, 2) The carcinogen of other origin, the « initia-

TABLE IV

Estimated total population by age in the Netherlands in 1929, 1939 and 1949, and in England and Wales in 1949 (Figures given to nearest thousand)

Age	Netherlands **			England and Wales * Mid year 1949	Ratio Neth. England and Wales in 1949
	Mid year 1929	Mid year 1939	Mid year 1949		
0 24	3 842	4 026	4,510	15,415	1 3 4
25 34	1,194	1 403	1,469	6 516	1 4 4
35 44	946	1 159	1,321	6 820	1 5 2
45 54	766	901	1 089	5 801	1 5 3
55 64	556	687	806	4,517	1 5 6
65 74	327	422	523	3,192	1 6 1
75 84	127	160	208	1,319	1 6,3
85	19	21	29	205	1 6,8
All ages	7,776	8 781	9 956	43,785	1 4,4

* Register General s Stat Rev of England and Wales for the year 1949
** Annual mortality statistics of the Centraal Bureau voor de Statistiek, The Hague

ter », might be atmospheric benzpyrene Various other materials, e g those ingested with our food — remember the lung tumours in mice after ingestion of urethane — might also act as initiaters

Finally we must admit the possibility that co operation of very weak carcinogens in tobacco smoke and weak carcinogens of other origin might start lung cancer

This way of reasoning indicates that it would be unwise to concentrate our attention too much on attempts to trace an actual carcinogen in tobacco smoke It also explains why, notwithstanding the noxiousness of tobacco smoke, a close parallel between the amount of tobacco consumed and the frequency of lung cancer need not exist E g tobacco consumption in the Netherlands greatly exceeds that in England, whereas the frequency of lung cancer in England is higher than in the Netherlands Possibly the much greater pollution of the atmosphere in England could account for this difference The initiater of lung cancer might be stronger in England, and the promoter in the Netherlands

*
* *

The final results of treatment of cancer of the lung are distressingly bad (9), and will in future probably deteriorate further (See my paper « Some remarks on the age curve in lung cancer ») On the other hand from the fact that a close statistical relationship exists between heavy smoking and lung cancer, it may be assumed that, through the pre- [illegible] heavy smoking, [illegible] reduce the endemic di- [illegible] account we should seriously ask ourselves whether we are any longer justified in continuing to maintain silence and in omitting to warn the public strongly against the great danger incurred by heavy smoking

When seeking the answer to this question we should not forget that, to give an example, at this very moment, in England and Wales more than *400 000* men (*) *and also a* large number of women are, by their heavy smoking, preparing the ground for lung cancer, the disease to which they will all fall victim, some of them already this year and others after many years (2, 10, 11)

Personally, I have no doubt as to what the answer to this question should be (2, 12)

During the last two years I have often lectured on this subject In my experience it is easier to persuade the public that heavy smoking is dangerous than to induce a smoker to draw the only possible conclusion therefrom I have also experienced however, that such an earnest appeal does find response in many Therefore, for defeatism there is no reason at all

DISCUSSION

Dr Hammond Were the cases screened in Holland unselected or were they patients with symptoms ? Were the cancers which were diagnosed, early or late ? We think of doing the same thing in the United States

Dr Korteweg They were absolutely unselected and we are trying to examine the whole population We found some early and some very advanced inoperable cases The early cases were treated surgically

Dr Hammond How many operable cases were found per 1000 ?

Dr Korteweg I am afraid I don't know but this is a very important question It may be that some lung cancers are very slow in developing and perhaps we ought to repeat the screening after a year or two

Dr Stewart All the evidence suggests that lung cancer is a very rapidly fatal disease

Dr Korteweg Yes but I know of at least one case which was diagnosed and [illegible] osis [illegible] two

Dr Maisin This must have been a very exceptional case In 300 cases I have seen myself it has always been a rapidly fatal disease

Dr Kretz We have also noted cases with undoubted lung cancer who have lived more than 1 1/2 to 2 years

(*) 16 000 times 25 16 000 being the estimated number of lung cancer deaths in males per annum and 25 the number of years of heavy smoking before lung cancer arises

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DR CLEMMESEN The length of survival will surely depend on the stage at which diagnosis is made If the pre-symptom period is included survival is longer Similarly, U S screening series of other cancers have shown some cases without symptoms Some of these refused operation and survived much longer than was expected

DR HAMMOND In Dr Graham's study of old T B X-ray plates he found many cases of lung cancer which had been undiagnosed at the time A few cases seemed to develop very slowly at first and then became rapidly fatal

DR DOLL The experience of mass miniature radiography in Britain is perhaps relevant We now examine 1 1/2 million people per annum The cases should be a sample of the general population, but probably some doctors encourage patients with symptoms to go for X-ray Dr Smith at the Ministry of Health is studying these figures and finds at ages 45 to 60, 77 tumours per 100 000 men and at ages over 60, 226 tumours per 100 000 men Some attempt is being made to see if early diagnosis improves prognosis but the findings so far are disappointing

DR DORN Does Dr Doll think that all cases discoverable by X-ray are being picked up ? If so you would be approaching a true incidence figure

DR DOLL The rate may be inflated by general practitioners sending suspected cases for Roentgen-examination Also the standard of radiological diagnosis certainly varies from unit to unit

DR HAMMOND Would it be more likely to give a prevalence figure The discouraging thing is that in all these screening series many of the cases are at a very late stage

DR MORGAN I would like to mention one case We do a routine chest X ray examination of employees and in May one man had a clear X ray In June he was admitted to hospital for pneumonia and was found to have a large growth

DR NEURDENBURG In Holland we are planning how to organize mass screening for early cases of cancer We do not know whether to use the Tuberculosis Organization and its mass screening or to set up a new one It may be the best idea to add cancer specialists to work with the T B screening organization

DR STEINER Dr Korteweg's curves showed a dip for lung cancer in 1945 and for all other cancers a year later Does not this merely indicate that most other cancers live longer from the onset of symptoms ?

DR DOLL Between 1943 and 1945 the con [illegible]

[illegible] land than in Norway

DR HAMMOND If I understand the implication of that correctly, the fall in cigarette consumption coincided with the drop in the curves for lung cancer

DR DOLL In Norway and Holland the drop in mortality does occur about two years after the drop in cigarette consumption, but it is too short a period for the two factors to be inter-related

DR KORTEWEG I asked at the Hague for figures of cigarette consumption during the war, but was told those for 1945 to 1946 were unreliable Your tobacco consumption was low during the war, but we had none at all

DR STEINER Could not the same be said of effects from gasoline and other agents during the war years ?

[illegible]

cessary to take into consideration the very difficult working conditions faced by the Dutch medical profession, for example a thing like shortage of X-ray films The fall may not have been due to lack of cigarette smoking In Denmark there was a change to the worse in the quality of tobacco, whereas according to tobacco manufacturers the increase in cigarette smoking since the war has been due mostly to the extension of the market to women There will certainly have been a fall in the petrol consumption in Denmark during the war Burning of coal and coke also decreased, and the consumption of substitutes like peat and brown coal and briquettes was raised, so that atmospheric pollution will have increased during the war

DR HAMMOND · The reason I raised the question was that we are often working on studies made twenty years ago We got an X-ray film showing a lesion that had not been diagnosed and years later the patient came in with lung cancer. Professor Maisin told us it developed very rapidly — that is a different point of view. We have evidence of an increase in smoking and use of gasoline two years before the lung cancer rate went up That does not prove anything, but we should look into it.

DR MAISIN I do not think there is a difference of view between us In saying the evolution of lung cancer was rapid I was speaking of single clinical cases Maybe in a large-scale X-ray survey when you are detecting pre-cancer, it may take twenty years to develop I think we experimental people should think not only in terms of carcinogens, but also in terms of existing carcinoma The evolution may *of course vary very much from one* patient to another, but speaking of carcinoma of the lung our experience teach us that generally speaking the evolution is a rapid one after the clinical discovery of the tumour Moreover it is possible that if a patient with

with experimental animals subject to various doses of carcinogens

DR KRETZ This problem of cocarcinogens is very important I would like to know whether substances other than croton oil are known

DR MAISIN It depends on the significance you are going to give to cocarcinogens For example estrogen is sometimes considered as a cocarcinogen If you take a male belonging to the 37 strains of mice and paint it with benzpyrene or methylcholanthrene you do not get cancer If you inject the male mouse with estrogen and paint it you get cancer If you inject estrogen alone you do not get cancer Thus we are not allowed to consider estrogen a cocarcinogen We know on the other hand that *methylcholanthrene* is a true cocarcinogen So the time has come to think not only of carcinogens but of cocarcinogens There exist a great variety of cocarcinogens besides the oestrogens *which in our mind are* cocarcinogens and not carcinogens, *every one know* that croton oil for example is a real cocarcinogen

DR STEINER *Professor Maisin's* comments are very important We have been talking in terms of single carcinogens — even then the problem is difficult It is still more complex when we have to think in terms of possible *cocarcinogens or* even epicarcinogens This makes it far more complicated

DR LEVIN *There seems to be two* different questions as regards duration *One* is how long the carcinogen must be applied The other is the length of the latent period after the carcinogen has been applied The data of Dr Doll and Hill show quite distinctly that the presumed carcinogenic effect of tobacco *smoke is proportional to the total dose of to*bacco throughout the period it was taken Some of our data show a similar relationship

DR DENOIX Dr Neurdenburg demonstrated a very large difference between France

be
or

diagnosis The overall rate for the Netherlands is *26 to 6 and for Paris and the surroun*ding area it is 27 to 9 These are very similar Taking the age group 65 to 69 the Netherland's figure is 146 to 5 and the Parisian figure 145 to 2

DR NEURDENBURG But we have a diffe-

sal factor producing the higher figure in towns or it may be just a question of better diagnosis

DR DENOIX *This seems to be a further* illustration of the difficulty of comparing figures without knowing all the facts

DR STEINER *The information coming to* light about the difference between town and country is just what we want The question arises — is it a real difference ? The only

way to get an answer is to do a series of screening studies on the same population The first screening will not be adequate as it will give an inflated figure

DR MAISIN It is very important to know if there is a real difference between town and country If we think there are causal factors such as smoke and dust in urban environ ments it is very likely there is a real diffe rence

DR NEURDENBURG We are doing T B surveys in town and country in Holland We

DR STEINER The critical information will be obtained at the third or fourth screening

DR CLEMMESEN Screening has been going on for some time all over Denmark In dis cussing the variation between town and coun try we must define what is meant by an ur ban and a rural area and the definitions will vary with the country When we use the dif ferences between men and women as a con trol we can show I believe that although there might be diagnostic differences these will only be small in comparison with the real differences

DR HAMMOND Dr Steiner's suggestion is a very constructive one and I hope that plans can be made to supplement it before the end of the conference We should need very large populations and therefore would need cooperation between a number of centres

DR CLEMMESEN We might persuade the W H O tuberculosis centre to extend their interest to cover cancer of the lung in all the countries where they work

MR WALLER On the difference between town and country Dr Stocks made a study of 30 large towns in Great Britain in 1921 to 1930 The death rates showed great diffe rences between the towns In 1946 to 1949 the differences had been somewhat reduced The lower ones have risen so that there is now more uniformity This tendency may be due to improved all round diagnosis or to some causal factor becoming more generally distri buted e g cigarette smoking

DR LEVIN Dr Steiner's s

ry important We could make screening stu dies of people living in different types of area But in the U S this would not have much meaning because of the great mobility of the population This causes difficulty to day in all epidemiological surveys Perhaps this could be overcome by taking residence histories

DR HAMMOND We ought to select for such a survey a country where the movement of the population has not been so great as in the U S A it should be easy to get a rural population where people had never lived in towns But in the urban series we should have to watch for people who had only moved into town on retirement

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place

DR CLEMMESEN We can easily trace peo ple in Denmark through the people s regis tries It is probably the same in other small countries

DR NEURDENBURG In Holland since shortly before the war a card is made up for each individual at birth and for each person living at the start of this system This card is kept by the registrar where the person li ves and follows him from residence to resi dence as his paper shadow and includes the refore a record of each residence through li fe This will be very useful in the future as all cards are collected by the Central Bureau of Statistics at the moment of death

duration of the pre-clinical period

DR HAMMOND In the study started by
[illegible]
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index case was then examined history, and environment etc recorded and followed for the past 25 years A study of the same gene ral nature has been proposed for lung cancer The area was chosen 25 years ago as it had the highest T B rate in the States and the

budget is over 100 000 dollars per annum Yet the population is not nearly large enough for a cancer study, and I would suggest that for a cancer study we must select the most *suitable areas* in town and rural areas and cooperate between different countries This will reduce the numbers needed and the cost

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ZUSAMMENFASSUNG

Der Verf gibt einen Ueberblick uber die Entwicklung der Mortalitat des Lungenkarzinoms in den Niederlanden seit 1924 und bespricht die Statistiken aus den Spitalern und von den Tuberkulose Reihenuntersuchungen Zahlenmassig werden die Rauchergewohnheiten erfasst und Vergleiche angestellt mit den entsprechenden Zahlen aus England Der Verf glaubt, dass der Tabakrauch die Entstehung des Lungenkarzinoms auslose das durch andere Faktoren bedingt ist, wie z B Benzpyren in der Luft und es werden die moglichen Konsequenzen dieser Ansichten diskutiert Er legt besonderes Gewicht auf die praktische Bedeutung einer Stellungnahme zu den Zusammenhangen zwischen dem Rauchen und dem Auftreten von Lungenkarzinomen Er weist nachdrucklich auf die Zukunftsaussichten hin und fragt sich, ob es auch weiterhin erlaubt sei Stillschweigen zu bewahren und das Publikum nicht ausdrucklich auf die grossen Gefahren des starken Rauchens aufmerksam zu machen

SUMMARY

The author gives a survey of the development with regard to mortality from cancer of the lung in the Netherlands since 1924, and discusses figures from … tuberculosis … smoking and … material from … smoke from tobacco might promote the genesis of cancer of the lung initiated by other factors such as atmospheric benzpyrene, and discusses the possible consequences of this suggestion He points to the necessity of practically taking an attitude to the interrelation between the smoking of tobacco and cancer of the lung Dr Korteweg *points to the serious prospects for the future* and asks whether it is defensible to continue in maintaining silence and in omitting to warn the public strongly against the great danger involved in heavy smoking

RESUMEN

El autor hace una comunicacion sobre la evolucion de la mortalidad por cáncer pulmonar en los Paises Bajos desde 1924 y comenta las cifras provinientes de los examenes masivos para el descubrimiento de los casos de tuberculosis Expone ademas cifras que expresan los hábitos de fumar y las compara con las correspondientes de Inglaterra

El autor piensa que el humo de tabaco podria estimular la aparición del cáncer pulmonar cuando otros estimulos iniciales hubiesen actuado tales como el benzopireno atmosferico y comenta las consecuencias posibles de estas sugerencias Insiste sobre la importancia practica que tendria en este problema de la interrelación entre el hecho de fumar y el cancer pulmonar, el autor pone de manifiesto la importancia de la evolucion del fenómeno en los años venideros

y se pregunta si puede seguirse callando sin llamar seriamente la atención del publico sobre el peligro que corren los grandes fumadores

RESUME

L'auteur fait un rapport d'évolution de la mortalite due au cancer du poumon dans les Pays Bas depuis 1924 et discute les chiffres provenant des hôpitaux et d'examens massifs pour la détection des cas de tuberculose Il donne encore des chiffres exprimant les habitudes de fumer et les compare à des chiffres correspondants provenant d'Angleterre

L'auteur pense que la fumee du tabac pourrait stimuler la genèse du cancer du poumon qui aurait trouvé son stimulus initial dans d'autres facteurs, tel le Benzopyrene atmospherique et il discute les conséquences possibles de cette suggestion Il insiste sur l'importance pratique qu'il y aurait a prendre position dans ce problème de l'interrelation entre le fait de fumer et le cancer du poumon L'auteur met en évidence l'importance de l'évolution du phenomene dans les annees futures et se demande si le silence reste permis et si l'on peut persister a ne pas attirer sérieusement l'attention du public sur le danger que courent les grands fumeurs

RIASSUNTO

L'A fa un rapporto [illegible]

[illegible] corrispondenti dati inglesi L'A ritiene che il fumo del tabacco possa stimolare la genesi del cancro del polmone, iniziatosi per altri fattori, quali il benzopirene atmosferico e discute tutte le possibili conseguenze di questa sua idea Egli evidenzia la necessità pratica di prendere finalmente posizione sulla correlazione di fumare e la eventuale insorgenza del cancro del polmone L'A mette in evidenza l'importanza della evoluzione di questo fenomeno nel futuro e si domanda se sia permesso continuare a mantenere il silenzio e non mettere in guardia il pubblico sul grande pericolo in cui possono incorrere i forti e fortissimi fumatori

Il nous a eté impossible par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Resumes

Nous le regrettons et nous en excusons vivement

La Redaction

A SURVEY OF THE HISTOLOGICAL TYPES OF ONE HUNDRED PRIMARY EPITHELIAL LUNG TUMOURS IN NORWAY (*)

BY

Leiv KREYBERG,

presented by K ARNESEN

(Universitetets Institutt for Generell og Eksperimentell Patologi Rikshospitalet Oslo Norway)

In many countries the statistical reports show a steady and remarkable increase in the *number of deaths from « lung cancer » The* problem puzzles the cancer specialists and troubles the public and the medical profession Does this increase signify a real augmentation of cases of lung cancer or does it simply mean an increasingly better diagnostical service ? This question will not be discussed in this paper

If we wish however to study the possible role of certain irritants in the genesis of lung cancer through statistical methods we have to make clear what we mean by the term « lung cancer »

According to KENNAWAY and KENNAWAY (1947) their statistics from England and Wales comprise « Cancer carcinoma or sarcoma of lung bronchus pleura root of lung *hilum of lung lung and mediastinum or* lung and pleura Pulmonary or bronchial carcinoma or sarcoma Cancerous pleur sy »

The official Norwegian mortality statistics has up to the publication of the latest figures *followed a similar pattern* with minor changes during two different periods

It is however not probable that all the morbid conditions included are caused by or influenced by the same factors Primary car*cinoma of pleura is a* very rare condition and would not disturb our statistics significantly Malignant diseases of the hilum of the lung on the other hand may include malignant lymphomas reticulosarcomas Hodgkins disease and other malignant or semima

(*) Condensed from a paper in press (Brit J Cancer Vol 6 p 140 1952)

lignant diseases In the group « lung cancer » may also be included a number of neurinomas *and* even an unknown number of infectious lung diseases

It is therefore with great satisfaction we acknowledge the fact that World Health Or

since the first of January 1951 acted accordingly It is a great step foreward

In order to

between lung

or industrial

tance not only to exclude all other lung tumours than primary lung carcinomas but even to subdivide the latter into special subgroups

From our general experience in the field *of cancer research we are ever more* impressed by the importance of the study of the geographical distribution of the different manifestations of malignant diseases This different geographical distribution examined on the background of the corresponding diffe

For these reasons we have embarked upon a *long time project in mapping* the occurrence of lung carcinoma in Norway with the first main object to examine the types of lung tumours most prevalent and next examine

series of stud

dred consecutive cases of primary epithelial lung tumours, received for diagnosis at the Institute of Pathology at the University of Oslo All, but also only those, tumours are included, where the piece of tissue was large enough to permit a definite histological classification The main part of the material (97 cases) was received from the Surgical Department A, at the University Hospital, 2 cases came from the Ear-Nose and Throat Department, and 1 case from the Roentgen-Radium Department Hereto are added 5 cases of secondary lung tumours, received within the same period, and clinically regarded as primary tumours, the histological examination, however, revealing their true character (2 cases of metastasizing thyroid adenoma, and 1 case each of hypernephroma, adenocarcinoma of uterus and malignant naevus tumor)

The one hundred tumours of the main series were classified according to traditional terminology as follows

A *Adenocarcinoma* has been the designation when a clear cut atypical, infiltrating cylindrical epithelium is present, with, or without, mucous secretion In a few cases special adenocarcinomas have been grouped, as stated below

B *Squamous Cell Carcinoma* includes tumours with a more or less marked stratification, or whorl formation of the tumour cells, or when keratosis or parakeratosis is present, or epithelial bridges can be seen In a small, but not insignificant number of cases, pictures may be found, presenting adenocarcinoma in one area and squamous cell carcinoma in another These cases have been placed in the intermediate group (AB) Every experienced pathologist will agree that borderline cases exist, and that, accordingly subjective factors may explain a different classification even of the same material In the present group controversy may especially arise as to the classification of squamous cell carcinoma, « highly atypical », on one hand, and the following on the other

C *Large Cell Carcinoma* This group comprises tumours with large atypical cells irregular growth and no differentiation

D *Small Cell Carcinoma* (« oat cell » tumour) represents an important group, with a characteristic microscopic picture, which, usually, does not offer greater diagnostic difficulties, if the material at hand is sufficient in size and properly fixed and stained In small pieces and in smears, or in badly fixed material, certain differential diagnostic difficulties may arise vis a vis a malignant adenoma

E *Papillary* and *Alveolar Carcinomas* form a small, but characteristic group of adenocarcinomas, the peculiar picture usually making

in our material representing 5 out of one hundred tumours The same types are encountered, as found in the parotid region, the mixed tumours, however, being rarer in the lung In some of the malignant tumours a definite adenocarcinomatous picture may be found, sometimes with a mucous secretion, but usually the pattern of the salivary gland tumours may still be recognized

G *Adenomas* are in most cases easily distinguishable by their trabecular or carcinoid pattern and with intermediate forms In our series 11 occurred Not a few develop towards malignancy, with metastases in the lymph nodes

The groups E, F and G do not show any marked preponderance in the one sex, or the other Further, these tumours are rather evenly distributed in the different age groups, and they occur even in very young people, our youngest patient being a girl of 19 with a malignant adenoma The papillary and alveolar carcinomas may have their specific, yet unknown, etiology The salivary gland tumours and the adenoma most probably originates from developmental irregularities

The groups A, B, and D in our material, in complete accord with general experience, show a marked preponderance of male sufferers, most marked in the small cell carcinoma and least in the adenocarcinoma These types of cancer are very rare before the age of forty, and they often show a very marked peak in the age group between fifty and sixty These are the tumours often designated bronchogenic carcinomas

The findings in the groups A, B, and D, comprising 81 tumours, have been compared to a material, ten times as large from Mayo Clinic, recently presented in four different papers by PATTON, McDONALD and MOERSCH (1951), CARLISLE, McDONALD and HARRING-

TON (1951), PATTON, MCDONALD and MOERSCH (1951, II) and MCBURNEY, MCDONALD and CLAGETT (1951) After having reduced the Mayo Clinic figures to the Oslo figure scale, the two materials are compared as to age and sex distribution The Mayo Clinic material comprises the same types of lung carcinomas as our groups A, B, C and D It is found that the two groups as to age distribution are practically identical

Quite another picture will be found when we examine the occurrence of the different tumour types I do not at all a priori accept this as a token of heterogeneity of the two materials, referring to my remarks above, as *to the strong individual factors involved in* the act of classification The homogeneity as to tumour occurrence in age groups seems to be more significant *Both* materials were of surgical origin

The figures from a recent Swedish report upon a surgical material of bronchogenic carcinoma, WIKLUND (1951), are rather similar *The distribution as to age groups is nearly* identical with the figures from Mayo Clinic and Oslo The sex difference is, however, still more pronounced, Dr *Wiklund* having *91,1* per cent males in his series As to the microscopic classification, he has adenocarcinomas 4,6 %, squamous cell carcinoma 62,9 %, undifferentiated carcinoma 25 1 % and uncertain type 7,4 % We have here another example, that the similarity is greater when we examine the materials on the basis of the more objective characteristic the distribution in age groups, than on the basis of the more subjectively influenced classification in histological types

It is evident that the surgical material cannot, without a closer examination be taken as representative for the occurrence and the distribution of lung carcinomas and lung tumours in the population First, cases occurring in old age will not be represented, as these patients are poor operative risks and seldom operated upon Secondly, at old age the diagnosis may be more difficult and possibly not pursued with the same enthusiasm as when the patient is a younger Thirdly, the sex distribution may be different It is not unlikely that the local doctor, the surgeon and the patient himself will take a greater risk and show a somewhat more heroic attitude towards the question of operation, when the patient is a male The *women in this* cancer age may possibly show more resignation as to the blows of fate Fourthly, a surgical material may show a greater number of benign and moderately malignant tumour types than the sum total This is significant when a material is examined including all primary epithelial tumours, but less important when *only* true bronchogenic carcinomas are concerned This underlines the importance of a carefull classification when statistics are to be compared The relevance of these remarks is partly confirmed through a study of a rather representative *post mortem* material from Oslo City Hospital (Ullevål Hospital) The figures have through the kindness and courtesy of Dr ARNT JAKOBSEN been placed at my disposal The material comprises 122 cases (82 males and 40 women) of primary « lung cancers » histologically verified, but not histologically classified, during the period (1937-46)

The sex ratio in this autopsy material is male female — 2 1, which is considerably closer to the sex ratio in our general mortality statistics (also very near 2 1 up to the last two years), than in my surgical material, *where the ratio was 4 1 (78 22) in the whole* group, and nearly 5 1 in the sub-group of pure bronchogenic carcinomas As was anticipated, a considerable number of cases were found in the higher age groups The occurrence of a certain number of cases in the early age groups indicates that a few adenomas are included also in the post mortem series

I wish to emphasize that the present paper [illegible]

[illegible]

tain interest First the [illegible] confirm the general impression that in Norway *the preponderance of the male sex in the* lung cancer statistics is not as marked as in many other countries Secondly, the occurrence of lung tumours *in surgical material in* different countries may represent fairly comparable material, but they differ widely from the actual occurrence in *the population total* as it may be found in autopsy material Thirdly, up to the present time the general mortality statistics are so unprecise that they must be used with great reservation as a base for the study of the actual occurrence of lung cancer In the present clinically select material of 105 cases of clinically primary lung cancers, 5 were shown to be secon-

dary and in 19 cases the tumours belonged to types where external irritants most probably do not play any role at all

DISCUSSION

DR CLEMMESEN Dr Kreyberg's results

term basis

DR MAISIN *If the Norwegian figures are* real then there is a very large difference be tween your country and Great Britain and the United States What is the reason for this very marked difference ?

DR NEURDENBURG In both the U S and British long term studies no questions have been included on other bad habits — such as alcoholic consumption etc

SIR ERNEST KENNAWAY We started work with the Norwegians precisely because of the difference in their sex ratios Comparisons should be made between Denmark and Nor way , there are difficulties with Sweden

DR ARNESEN *We can as yet give no ex*planation for our figures So far we have only mortality rates but we shall begin to get more information through our cancer registry I think I should say that our diagnostic facilities do not cover the population as well as those in Denmark They are least good for the farmers and fishermen in the North

DR HAMMOND With regard to Dr Neurdenburg's question we can only get answers to a certain number of questions We tested out questionnaire first to see what was feasible

DR CLEMMESEN Some explanation of the Norwegian figures may be that there is a smaller *proportion of the population in big* cities For instance Copenhagen comprises 1/4 of Denmark's population and provincial towns another quarter

SIR ERNEST KENNAWAY In Norway 28 per cent of the population live in cities

ZUSAMMENFASSUNG

Es wird ein vorläufiger Bericht über 100 aufein

wie in vielen anderen Ländern

Der Verf legt besonderes Gewicht auf die Unterschiede zwischen dem Sektions- und dem Operationsmaterial und er empfiehlt die allgemeinen Sterblichkeitsstatistiken mit einer gewissen Zurückhaltung zu betrachten

SUMMARY

A preliminary survey is given of 100 consecutive primary epithelial lung tumours from Norwegian hospitals The cases are histologically classified and the distribution by sex and age is discussed It is concluded that in Norway the preponderance of the male sex in statistics on cancer of the lung is not as marked as in many other countries The author stresses the differences between autopsy material and surgical material and recommends some reservation in the use of statistics on general mortality

RESUMEN

El autor hace una primera exposición de 100 casos consecutivos de tumores epiteliales primarios del pulmon procedentes de hospitales noruegos

Los casos han sido agrupados histologicamente y el autor comenta su distribución segun el sexo y la edad El autor concluye que en Noruega las estadisticas no poenen de manifiesto el predomino del cáncer pulmonar cono ocurre en otros muchos paises

El autor insiste sobre las diferencias observadas entre el material de autopsia y el quirurgico y pone de manifiesto las reservas que deben ser tenidas en cuenta al utilizar las estadisticas sobre mortalidad general

RESUME

L'Auteur fait un premier rapport de 100 cas consecutifs de tumeurs épitheliales primaires du poumon provenant d'hôpitaux norvegiens

Les cas ont été groupes histologiquement et l'A discute leur distribution suivant le sexe et l'age L'A conclut qu'en Norvege, les statistiques ne mettent pas en évidence une predominance du cancer du poumon comme c'est le cas dans de nombreux autres pays

L'A insiste sur les différences observées entre le materiel d'autopsie et le materiel chirurgical , il met en evidence les réserves dont il faut tenir compte dans l'utilisation des statistiques sur la mortalite générale

RIASSUNTO

L'A. ha riferito su una rassegna preliminare di 100 casi consecutivi di tumori epiteliali primitivi del polmone osservati negli ospedali norvegesi. La casistica è classificata dal punto di vista istologico ed è discussa in rapporto all'età ed al sesso. L'A. conclude che in Norvegia la prevalenza del cancro polmonare nel sesso maschile non è così accentuata come in molti altri paesi.

L'A. insiste sulle differenze osservate nel materiale autoptico in confronto a quello chirurgico e sottolinea le riserve che debbono essere tenute presenti nella valutazione delle statistiche sulla mortalità generale.

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés.

Nous le regrettons et nous en excusons vivement.

La Rédaction.

MORTALITY AND INCIDENCE OF CANCER OF THE LUNG IN DENMARK AND SOME OTHER COUNTRIES

BY

Johannes CLEMMESEN, Arne NIELSEN and Emmerik JENSEN
(The Danish Cancer Registry under the National Anti Cancer League, København ö, Denmark.)

A considerable number of authors have from time to time analyzed materials of cases of cancer of the lung from various sources

months advocated the view that this increase in numbers is only apparent, caused by increased medical attention and by improvements of diagnostic facilities Also improved therapy of pneumonia which often complicate early cases of carcinoma of the lung has been said to increase the chance of correct diagnosis, because the life of the patient is preserved until the tumour is sufficiently large to be recognized with certainty

One important reason why this discussion has lasted for decades is that materials for analysis have nearly always been collected from hospitals or other medical centers serving populations of unknown delimitation Under such conditions it is nearly impossible to ensure that increase in the number of cases admitted for treatment of a certain disease is not caused by unknown changes in the population served, not to speak of selection due to increased attention, better diagnosis etc In order to establish a proof of the reality of the increase in incidence of cancer of the lung, and open the way for further research, it will be necessary to study a population, well delimited and of sufficient size, uniform and fairly stationary socially, economically, and with regard to living place Medical facilities of best quality should be equally accessible to all social strata of population, and statistical facilities should be of a corresponding standard

We believe that the material from Denmark will be able to fulfil these requirements Indeed, one of the tasks mentioned at the opening of the Danish Cancer Registry in 1942 was the assessment of the nature of the increase in the number of male deaths ascribed to cancer of the lung

The Rise in Mortality from Cancer of the Lung in Denmark since 1931.

Figures 1 and *2* give crude mortality rates respectively for men and women for cancer of the lung in Danish Capital, provincial towns, and rural areas based partly on hitherto unpublished figures of the National Health Service for 1931 to 1950 It appears that while the figures for the two sexes in 1931 were almost identical, being for men respectively 4 5, 2 1, and 1 6, and for women 3 7, 1 7, and 0 9, there is a considerable difference for 1950 when figures amounted to respectively 36 9, 13 5, and 10 1 for men and 5 3, 3 4, and 3 9 for women

The increase in mortality rates seems to have taken its beginning about 1931 for men in Copenhagen, and respectively about eight and ten years later for men in provincial towns and rural areas

The curves for women are nearly horizontal apart from a slight but significant rise following 1940, corresponding to the increase in steepness of the graphs for men at the same period which was characterized by improvements in diagnostic facilities It should be noticed that this increase is found for both sexes, as one will expect from an increase caused by diagnostic improvements, while the major part of the slope represents an increase for men only and therefore cannot very easily be explained as caused by

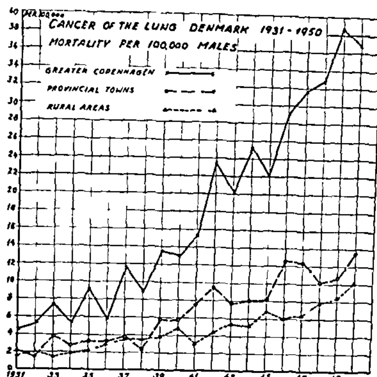


Fig 1

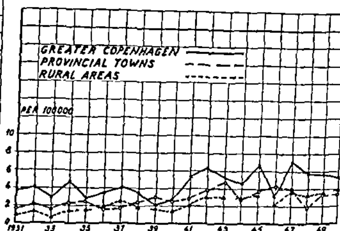


Fig 2

TABLE V

Cancer of Larynx and Trachea (161 and 162,0), Denmark 1931-50 — Number of deaths and crude mortality per 100,000 population

Year	MALES		FEMALES	
	Number	Rate	Number	Rate
1931*	26	1 5	15	0 8
32*	26	1 5	5	0 3
33*	22	1 2	2	0 1
34*	19	1 1	6	0 3
35*	21	1 2	9	0 5
1936*	20	1 1	5	0 3
37*	24	1 3	5	0 3
38*	13	0 7	3	0 2
39*	25	1 3	12	0 6
40*	[illegible]	1 2	5	0 3
1941	31	1 6	5	0 3
42	19	1 0	7	0 4
43	23	1 2	5	0 3
44	19	1 0	5	0 2
45	24	1 2	5	0 2
1946	22	1 1	8	0 4
47	20	1 0	10	0 5
48	18	0 9	—	—
49	[illegible]	1 4	7	0 3
50	29	1 4	3	0 1

* 1931 40 exclusive cancer of trachea.

diagnostic improvements Because some authors regard it as impossible to tell how much of the increase in frequency of cancer of the lung should be ascribed to progress *in diagnostic methods, and how much to a* real increase in the extension of the disease we would like to point to this possibility of distinction

[illegible]

men than for women, but no increase in rates **

Men and Women

The slight excess of the figures for Copen hagen already seen for 1931 *(fig 1 and 2)* appears for both sexes, and may therefore be attributed to slightly better medical facilities in the capital, although it cannot be entirely excluded that factors causing the increase in deaths among men may have had some in fluence on both sexes already at this time On the whole, however, we would be inclined to accept the mortality figures for women as representing the « unavoidable » — perhaps endogenous — amount of cancer of the lung,

** For tables 1 4 see pp 206 208

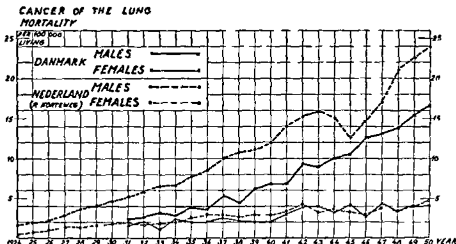


Fig 3

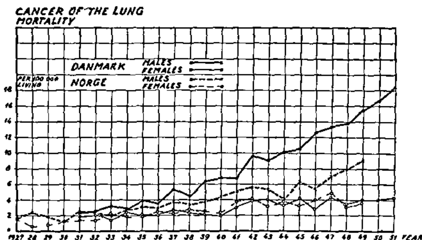


Fig 4

corresponding to the rates for men in 1931, before the rise in mortality began, so that the figures for women to some extent may serve as control

In this view we are supported by the crude mortality rates for the Netherlands from 1924 to 1950 (KORTEWEG 1952) and from Norway from 1927 to 1949 (15), which as far as wo
for Denr
judging f
if women do not necessarily show these low

out with full attention to the proportion of town- and country-dwellers in the various countries

TOWNS AND COUNTRY

With regard to the categories of towns in

Denmark it should be noted that in Denmark, as in various other countries, the category of provincial towns is largely historically determined so that even greater villages may surpass the size of urban communities of older age Since the subdivision of the population according to urban and rural community will play an important part in the following, the definitions are given below

By the term Capital is meant the conurba-

the latter largely being of a suburban character The populations in June 1945 amounted *to the following figures*

City of Copenhagen	731,707
Frederiksberg	113,584
Gentofte	82,113

The term Provincial Towns covers the categories of towns given in *table 6*

Table VI

In June 1945 the populations amounted to the following figures

Aarhus	*107,000*
Odense	92,000
Aalborg	61,000
10 *towns of more than* 20,000 inhabitants	276,406
16 *towns of* 10 20,000 inhabitants	235,277
14 towns of 7-10,000 inhabitants	*118,453*
5 *towns of* 5-7,000 inhabitants	31,993
16 towns of 3-5,000 inhabitants	*60,815*
8 towns of 2-3,000 inhabitants	18,717
13 towns of under 2,000 inhabit	18,773
	1,020,434

Rural Areas comprise the remaining parts of the country including 686,000 inhabitants *of sub-urban areas*

As indicated in fig 1 provincial towns show a rise in mortality from cancer of the lung similar to the rise for the capital, but beginning five to ten years later A special *analysis* for the three cities of Aarhus, Odense, and Aalborg showed no significant de*viation from the entire category*

The rise for rural areas beginning a full decade later than the rise for the capital fol*lows almost parallel* to the rise for provincial towns.

Conclusion

Mortality from cancer of the lung in Denmark shows an increase of rates *for men in* the capital beginning about 1931, and respectively eight and ten years later for provincial towns and rural areas During the years immediately after 1940, when lung surgery and systematic bronchoscopy were introduced, a slight rise in figures was observed for both sexes in the capital

Material of the Danish Cancer Registry.

The proof that the increase in deaths ascribed to cancer of the lung among males in Copenhagen is not caused by improvements of diagnostic methods must be produced by

here that the Registry is run by the National Anti-Cancer League for the purpose of studies of the endemiology of cancer The institute is not charged with therapeutical statistics nor with the task of follow-up, al- ... *orking in* ... the Re ... a volun- ... ssistance of many persons and institutions

Hospital doctors will report all cases of cancer admitted in hospitals, which mostly are closed hospitals run by municipal or county authorities, but also private hospitals participate in the scheme All post mortems performed on cases of cancer will be reported separately by the pathological institutes

The National Health Service assists in passing death certificates through the Registry, so that all cases which have not been cured will come to its attention

The National Statistical Office assists in giving full technical facilities for the hand*ling of our material free of charge*

TABLE VII

The Danish Cancer Registry 1943-47
Carcinomas of Bronchus and Lung (162 1 and 163) — Verification of Diagnosis.

FEMALES

	Year	All cases	Admitted in hospital Number		Histologically verified Number	per cent of all cases	per cent of hosp cases	Number of deaths	Autopsies Number	per cent of all cases	per cent of deaths	Grading of validity of diagnosis * per cent of all cases 1	2*	3	Total
Capital	43	27	25	93	18	6	7	26	21	78	81	81	4	15	100
	44	1	15	88	12	1	80	16	11	65	69	76	0	24	100
	45	23	1	91	1	5	57	23	15	65	65	0	4	26	100
	46	1	21	100	1	81	81	0	15	71	75	86	5	9	100
	47	31	25	81	15	48	60	30	14	45	47	61	10	29	100
	Total	119	107	90	4	6	69	115	76	64	66	74	5	21	100
Provincial Towns	43	10	8	80	4	40	50	9	5	50	56	50	0	50	100
	44	11	9	82	7	64	78	11	3	27	27	64	0	36	100
	45	10	7	0	3	30	43	10	1	10	10	30	10	60	100
	46	16	11	69		19	27	16	3	19	19	25	6	69	100
	47	15	12	80	6	40	50	12	3	20	25	40	7	53	100
	Total	6	47	6	23	37	49	58	15	24	26	40	5	55	100
Rural Areas	43	27	1	63	8	0	47	27	5	19	19	33	4	63	100
	44	24	16	67	8	33	50	24	5	21	21	42	0	58	100
	45	24	14	58	6	25	43	23	3	12	13	24	8	68	100
	46	24	16	6	8	33	50	19	4	17	21	33	0	67	100
	47	36	26	72	1	33	46	28	10	28	36	39	8	53	100
	Total	136	89	65	4	31	47	121	27	20	22	35	4	61	100

* According to Recommendation 1 of Louvain Symposium 195

TABLE VIII

The Danish Cancer Registry 1943-47
Carcinomas of Bronchus and Lung (162 1 and 163) — Verification of Diagnosis

MALES

	Year	All cases	Admitted in hospital Number	%	Histologically verified Number	per cent of all cases	per cent of hosp cases	Number of deaths	Autopsies Number	per cent of all cases	per cent of deaths	Grading of validity of diagnosis * per cent of all cases 1*	2	3	Total
Capital	43	96	90	94	61	64	68	94	62	65	66	72	5	23	100
	44	129	122	95	78	60	64	128	80	62	62	79	6	15	100
	45	120	111	93		60	65	118	72	60	61	74	8	19	100
	46	150	137	91	89	59	65	142	89	59	63	75	6	19	100
	47	172	159	92	112	65	70	162	98	57	60	74	4	22	100
	Total	667	619	93	412	6	67	644	401	60	62	75	6	19	100
Provincial Towns	43	39	31	79	11	28	35	39	12	31	31	38	3	59	100
	44	48	42	88	5	5	60	45	19	40	42	58	6	36	100
	45	43	40	93	5	59	62	39	18	42	46	0	14	16	100
	46	62	53	85	30	48	57	59	22	35	37	60	6	34	100
	47	60	50	83	29	48	58	41	13	22	32	52	8	40	100
	Total	252	216	86	120	48	56	223	84	33	38	56	8	36	100
Rural Areas	43	63	51	81	27	43	53	61	23	37	38	51	3	46	100
	44	47	39	83	27	57	69	45	19	40	42	64	6	30	100
	45	63	54	9	23	34	43	65	17	25	26	41	7	52	100
	46	58	44	79	9	52	66	52	20	36	38	59	2	39	100
	47	76	57	5	34	45	60	52	15	20	29	49	5	46	100
	Total	310	245	79	140	45	57	275	94	31	34	52	5	43	100

* According to Recommendation 12 of Louvain Symposium 1952

TABLE IX

The Danish Cancer Reg stry 1943 47

Carcinomas of Bronchus and Lung (162 1 and 163) Test for l near rise in morbid ty rates per 10 000 populat on

	Mean rate $\overline{m}$	Slope $\overline{b}$	Disper sion $\overline{b}$
Males			
Capital	3 08	0 36	0 084
Prov nc al Towns	1 03	0 0?4	0 046
Rural Areas	0 57	0 0 8	0 0 3
Females			
Cap tal	0 47	0 017	0 030
Prov ncial Towns	0 ?1	0 0?4	0 0?1
Rural Areas	0 ?	0 016	0 016

Tables 7 8 and *9* give the material of cases of carcinoma of bronchus and lung registered by the Danish Cancer Registry during the years 1943 to 1947

For each year it has been indicated how many cases were admitted in hospital and thus notified directly to the Registry while remaining cases were entered from death certificates

Furthermore is given the per cent of cases verified by histological examination or by autopsy It should be added that Danish hospitals are allowed to perform post mortem examination in all cases where objections have not been raised by relatives 12 hours after the receipt of a message of death which entails a fairly unbiased sampling of cases for autopsy

In order to make information as complete as possible a special revision of the material was carried out for Copenhagen for the years 1943 to 1947 checking case records for information when this was found to be incomplete This revision caused no significant change of figures except that the number of well examined cases proved higher than hitherto assumed

Conclusion

The material of the Danish Cancer Registry shows a statistically significant increase in incidence for carcinoma of the lung among men in Copenhagen from 1943 of 1947 During this period the per cent of cases admitted in hospital and the per cent of cases verified by histological or post mortem examination remained constant Therefore the increase in rates cannot be due to application of these fundamental diagnostic means to a higher per cent of cases Throughout this period the grade of validity of diagnosis constantly amounted to about 75 per cent

Social Distribution

In order to examine more in detail the distribution of cases of carcinoma of the lung within Greater Copenhagen we have made use of a study by CLEMMESEN and ARNE NIELSEN (1951) on the social distribution of cancer within that city

For this study all cases of cancer occurring during the years 1943 to 1947 were distributed according to living place at the time of diagnosis The area of Gre t C [illegible]
had bee [illegible]
each of [illegible]
able on [illegible]
as well as on the average house rent for 1940 which at the time in question was an adequate indicator of the social standard for a family [illegible] las [illegible] *11* [illegible] of [illegible] their inhabitants

It appears from *table 12* that the basis of the diagnosis is on the whole the same for all parts of the town

An analysis of the incidence of carcinoma of the lung in the five classes of subdistricts shows that this cancer will increase in frequency among men with a lowering of the social level in almost the same way as cervical uterine cancer among women from the same period

It is an outstanding feature that class II shows a surplus of cancer for both sites Since it is difficult to assume that the same factor should equally influence two types of cancer predominent in different sex it is nearer at hand to look for an irregularity in the common stratificator i e the house rent

This assumption is in accordance with the fact illustrated in *tables 13* and *14* that cervical cancer shows the same age distribution in all classes of subdistricts while pulmonary carcinoma in class II like in other classes of high incidence has relatively many cases in younger age classes

TABLE X

The Danish Cancer Registry 1943-47
Bronchogenic Carcinoma
Diagnostic procedures in classes of subdistricts according to house rent in Greater Copenhagen

Class of subdistricts House rent 1940	Hospital admissions in per cent	Histol exam. per 100 admissions	Autopsy per 100 deaths	Autopsy and Histol. exam. pr 100 cases	Bronchogen carcinoma males in per cent of standard value	Cervical carcinoma in per cent of standard value
I Gentofte 1440 kr	85	71	62	65	66	50
II Frederiksberg 1050 kr	88	77	63	77	107	92
Voldkvarter 1100 kr					75	83
III. Østerbro etc 850 950 kr	93	[illegible]	64	75	90	79
IV Valby, Sundby, etc 750-850 kr	93	68	56	74	97	100
V Indre By, Nørre Vesterbro 645 750 kr	96	62	63	76	116	131
Average	93	67	62	75	100	100

TABLE XI

Greater Copenhagen, 1940 and 1935
Populations in classes of subdistricts of identical house rent characterized by occupation and income

	Borough of Gentofte I	Borough of Frederiksberg Part of II	Municipality of Copenhagen: Vold kvarter Part of II	Municipality of Copenhagen: Østerbro III	Municipality of Copenhagen: Valby and Sundby IV	Municipality of Copenhagen: Old City Nørre Vesterbro V	Municip Copenhagen Total
Male breadwinners. Census November 5, 1940							
Independent or directing	24	18	—	—	—	—	11
All Officials	40	35	—	—	—	—	25
Workmen	27	36	—	—	—	—	55
Other or unstated occupation	9	11	—	—	—	—	9
Total	100	100	—	—	—	—	100
Males and females paying income tax 1935							
Independent or directing	—	—	14	11	8	9	10
All Officials	—	—	35	33	26	23	27
Workmen	—	—	27	41	56	53	49
Other or unstated occupation	—	—	24	15	10	15	14
Total	—	—	100	100	100	100	100

TABLE XII

The Danish Cancer Registry 1943 47 Capital
Cancer of Bronchus and Lung (162 1 and 163)
Verification of diagnosis in classes of subdistricts according to house rent

MALES

Class of Subdistricts	All cases	Diagnosed in hospital Number	%	Histologically verified Number	per cent of all cases	per cent of hosp cases	Number of deaths	Autopsies Number	per cent of all cases	per cent of deaths	Grading of validity of diagnosis per cent of all cases 1°	2°	3°	Total
I	40	34	85	21	60	71	40	25	62	62	65	5	30	100
II	120	105	88	81	68	77	113	73	61	65	77	2	21	100
III	121	113	93	74	61	65	117	75	62	64	75	7	18	100
IV	101	94	93	64	63	68	96	54	53	56	74	10	16	100
V	285	273	96	169	59	62	278	174	61	63	76	6	18	100
Total	667	619	93	412	62	67	644	401	60	62	75	6	19	100
FEMALES														
Total	119	107	90	74	62	69	115	76	64	66	74	5	21	100

TABLE XIII

The Danish Cancer Registry Capital 1943-47
Cervical cancer (171) in classes of subdistricts of identical house rent compared with computed standardized values

Class of Subdistricts	Age 39 Obs	Comp	Obs / Comp %	Age 40-49 Obs	Comp	Obs / Comp %
I	9	20 5	44	14	32 5	43
II	31	37 5	83	57	64 6	90
III	42	52 8	80	71	77 8	91
IV	41	48 1	85	69	59 2	117
V	114	77 9	146	143	119 5	120
Unstated	—	0 2	—	—	0 4	—
Probability		< 5 %			< 5 %	
	Age 50-59			**Age 60-**		
I	12	26 0	46	15	20 1	75
II	51	55 4	92	48	51 4	93
III	41	61 4	67	34	45 8	74
IV	40	39 7	101	29	31 5	92
V	139	100 0	139	113	89 9	126
Unstated	—	0 5	—	—	0 4	—
Probability		< 5 %			< 5 %	
	Total					
I	50	99 2	50			
II	187	208 9	90			
III	188	237 8	79			
IV	179	178 5	100			
V	509	387 3	131			
Unstated	—	1 4	—			
Probability		< 5 %				

TABLE XIV

The Danish Cancer Registry
Capital 1943-47
Cancer of Bronchus and Lung (162 1 and 163) in classes of subdistricts of identical house rent compared with computed standardized values

MALES

Class of Subdistricts	Age -54 Obs	Comp	Obs / Comp %	Age 55-64 Obs	Comp	Obs / Comp %
I	13	20 1	65	11	25 0	44
II	36	36 5	99	48	49 3	97
III	46	49 6	93	49	57 4	85
IV	39	40 5	96	43	42 1	102
V	95	81 2	117	128	104 3	123
Unstated	—	1 1	—	—	0 9	—
Probability		> 5 %			< 5 %	
	Age 65-			**Total**		
I	16	13 8	116	40	58 9	68
II	34	29 3	116	118	115 1	103
III	25	28 3	88	120	135 3	89
IV	18	22 2	81	100	104 8	95
V	60	59 1	102	283	244 6	116
Unstated	—	0 3	—	—	2 3	—
Probability		> 5 %			< 5 %	

Apparently the population in class II are inclined to spend relatively more on house rent than corresponding to their level of general conditions of health The analysis of

the figures given indicates that the area in question is the borough of Frederiksberg a municipality which keeps a lower level of taxation so that more money will be available on peoples budget for house rent

Histological Type

In order to examine if there is prevalence of any particular histological type of carcinoma in the districts where cancer of the lung is more frequent we have worked out *table 15*

TABLE XV

The Danish Cancer Registry
Bronchogenic Carcinoma Greater Copenhagen
1943-47
Histological Type given as per cent of all cases for classes of subdistricts of identical house rent

Class of Subdistrict	Adenomatous Type Per cent	Non Adenomatous Type Per cent	Type not determined Per cent	Number of cases
MALES				
I	10	50	40	40
II	12	58	30	120
III	11	54	35	121
IV	8	61	31	101
V	6	59	36	285
Total	9	57	34	667
FEMALES				
Total	24	40	36	119

It appears that in the districts where bronchogenic cancer is more frequent the percentage of non adenomatous forms is higher than elsewhere although the difference is not statistically significant This would seem to some extent to support the observations of Wynder and Graham which claim that the increase of bronchogenic cancer is due mainly to an increase of squamous cell carcinomata although some increase is observed also for adenomatous forms It should be pointed out that we have not ourselves examined slides of the tumours systematically and therefore have found it sound to refrain from a more detailed subdivision of the material because the criteria of pathologists may differ On the other hand it would seem safe to reckon on the uniformity in criteria of the categories adenomatous and non adenomatous forms even by various pathologists It is also in conformity with the findings of Wynder and Graham that the non adenomatous forms are far less prominent among women

If we analyze the distribution by age of bronchogenic cancer on the various parts of Greater Copenhagen we find — as already mentioned — that quarters with a high incidence will show a preponderance of cases in the younger age classes *(table 14)*

Larynx and Trachea

For the sake of completeness the incidence rates for carcinoma of larynx and trachea are given for various age classes separately for the capital provincial towns and rural areas (table 16)

Conclusion

It follows from studies on material from the Danish Cancer Registry that if the increase in male cases of carcinoma of the lung observed in Greater Copenhagen from 1943 to 1947 could be supposed to be apparent only it would have to be explained by increased medical attention applied in proportion to all categories of male patients — from the 75 per cent of cases subject to thorough examination to the seven per cent of cases not admitted in hospital and thus less well examined — but not to women

The incidence of the disease is particularly high in quarters with low house rent which also show a preponderance of cases in the younger age classes *(table 14)* Consequently it appears that only men and particularly those of the younger age classes and less well to-do could be supposed to have benefitted from such supposed increased realization of the real distribution of cases and this inequality in the real distribution of bronchogenic carcinoma would then have to be ascribed to exogenic carcinogenesis

One way finally to disprove the assumption that the increase in incidence of carcinoma of the lung is due to an increase in medical attention would be to follow the number of cases occurring among a number of persons examined by a uniform method primarily

TABLE XVI

The Danish Cancer Registry 1943-47.
Carcinomas of Larynx and Trachea (161 and 162,0)

MALES

Age	Number			Per 10,000 population			Total
	Capital	Provincial Towns	Rural Areas	Capital	Provincial Towns	Rural Areas	
29	—	—	—	—	—	—	—
30 34	1	—	—	0 1	—	—	0 0
35 39	3	—	—	0 2	—	—	0 0
40-44	2	3	3	0 1	0 2	0 1	0 1
45-49	5	5	8	0 3	0 3	0 2	0 3
50 54	9	6	7	0 7	0 5	0 3	0 4
55 59	12	3	5	1 1	0 3	0 2	0 4
60 64	8	7	9	0 9	0 7	0 4	0 6
65 69	10	6	8	1 4	0 7	0 5	0 7
70 74	5	3	11	1 1	0 5	0 9	0 8
75 79	8	6	5	3 0	1 7	0 6	1 4
80 84	—	2	4	—	1 2	1 0	0 9
85	—	2	3	—	2 7	1 6	1 6
Unknown	1	1	—	—	—	—	—
Total	64	44	61				

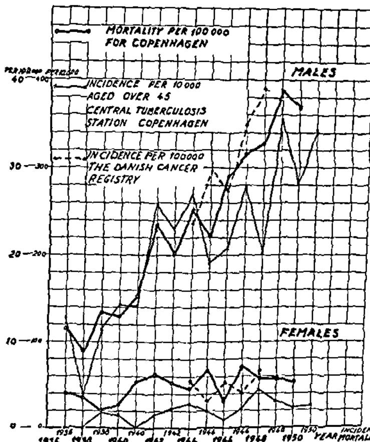


Fig 5

with a view to a different disease This can be done by means of a material from the Tuberculosis Station of the City of Copenhagen placed at our disposal by the courtesy of Chief Physician KNUD WINGE, M D

Material of the Central Tuberculosis Station of Copenhagen.

In 1947 CLEMMESEN and BUSK reviewed the material of Danish death certificates with a diagnosis of cancer of the lung from 1931 to 1945 They found a clear increase in the rates for men, most pronounced for the capital, less pronounced for provincial towns, and still less for rural areas For Copenhagen the figures for male mortality from cancer of the lung were tripled during the period from 1936 to 1945 However, records from the Central Tuberculosis Station of the City of Copenhagen on cases of bronchial carcinoma diagnosed among out-patients, referred for

was introduced in Copenhagen together with systematic bronchoscopy, both the mortality figures for Copenhagen and the material of the Tuberculosis Station showed a sudden increase *As far as the Tuberculosis Station*

TABLE XVII

Cancer of Lung (*)
Central Tuberculos s Stat on Copenhagen

	Males over 45			Females over 45		
	Examined	Cancer	Morbidity rate per 10 000	Examined	Cancer	Morbidity rate per 10 000
1936	466	6	128 8	487	0	0 0
37	593	2	38 2	58	0	0 0
38	526	6	114 1	581	1	17,2
39	630	9	142 9	667	1	15 0
40	568	8	140 8	6 7	0	0 0
41	696	18	258 6	690	1	14 5
42	916	21	229 3	878	2	22 8
43	967	26	268 9	1055	3	28 4
44	1056	20	189 4	1016	1	9 8
45	1057	22	208 1	1129	1	8 9
46	1545	43	278 3	1389	3	21 6
47	1679	34	02 5	1578	7	44 4
48	1246	44	353 1	1297	4	30 8
49	1318	37	80 7	1316	3	2 8
50	15 6	54	34 6	1567	4	25 5
Age	**Males 1936-40**			**Females 1936-40**		
	Examined	Cancer	Morbidity rate per 10 000	Examined	Cancer	Morbidity rate per 10 000
25 34	5547	1	1 8	8 89	0	0 0
35-44	2980	4	13 4	3860	0	0 0
45 54	1681	15	89 2	1 97	1	5 6
55 64	753	11	146 1	840	1	11 9
65 74	230	3	130 4	266	0	0 0
75	49	2	408 2	37	0	0 0
	Males 1941-45			**Females, 1941-45**		
25 34	8469	1	1	11624	0	0 0
35-44	4759	9	18 9	5841	1	1 7
45 54	2741	32	116 7	2765	1	3 6
55 64	1417	56	395 2	1435	4	27 9
65 4	435	16	36 8	490		40 8
75	99	3	303 0	78	1	1 8
	Males, 1946-50			**Females 1946-50**		
25 34	7210	3	4 2	10482	0	0 0
35-44	5263	11	20 9	6543	4	6 1
45 54	3724	64	171 9	3685	4	10 9
55 64	2404	109	453 4	2253	10	44 4
65 74	1012	32	316 2	1007	5	49 7
75	2 4	7	312 5	201	2	33,5

(*) Revised f gures

was concerned the increase in rates was pronounced for a single year after which the curve returned to a level between the peak and the original level

CLEMMESEN and BUSK concluded that even a pronounced increase in the crude mortality rate for cancer of the lung among males would not necessarily mean an increase in incidence of that disease

It will be understood by a glance at the curve in *fig 5* that the increase for men would appear more pronounced in relation to the slope in general when only the years up to 1945 are represented as in the studies of CLEMMESEN and BUSK from 1947 but the extension of the material with cases for five further years has now made it possible to regard these results in a wider context

On a revision of the material of the Tuberculosis Station taking full advantage of later

experience in diagnosis and later information on the ultimate fate of each patient it appeared that figures for later years were in fact higher than stated in 1947 The results of the revision will appear from *table 17*

In spite of the relatively small figures from the Tuberculosis Station these totals are representative drawn as they are from a population of about one million through a uniform and simple procedure designed for the detection of cases of a disease different from bronchial carcinoma but nevertheless covering a not inconsiderable part of the persons among which one might expect to find such cases of cancer of the lung which might have escaped discovery in days of less adequate diagnoses than now Cases are referred by the medical practitioner directly to the Central Tuberculosis Station where furthermore most of the difficult roentgen photos usually are seen by the same person The later fate of patients is followed by means of case records from hospitals death certificates and post mortem records

The curves of *fig 5* give the rate of deaths ascribed to cancer of the lung for Greater Copenhagen compared with the rate of cases found among persons aged over 45 examined in the Tuberculosis Station for the City of Copenhagen up to 1950 The limitation to the older classes of age was made necessary by the disproportionate number of examinations of young people made in the station

Since some time will pass between diagnosis and death the curve for cases diagnosed has been moved one year to the right in order to correspond to the mortality curve and f... 00 allo ... the pa ... ubercu losis Station for chest trouble

It is seen that given in this proportion the increase in number of deaths corresponds to the increase in the rate of cases found in the Tuberculosis Station The coincidence of the two curves would have been even closer had it not been for a campaign in 1948 of roentgen mass examination which probably deprived the material of the Tuberculosis Station for this period of a minor number of cases which were diagnosed by the campaign but under ordinary circumstances would have been referred to the Station for diagnosis

For the years following 1940 both curves show a steeper rise, the slope of which probably *is due to the* introduction of systematic bronchoscopy and other diagnostic improvements together with the increased attention following the organization of units for lung surgery in Copenhagen The absolute number of female cases *(see table 17)* are too small to allow conclusions

The curves for the Cancer Registry for 1943 to 1947 run parallel to the first two curves but at a higher level

Conclusion

Thus the material of the Central Tuberculosis Station is no longer an obstacle to the assumption that the increase in the number of deaths ascribed to cancer of the lung is caused by a real increase in the number of cases What is more This material which represents a sample chosen through a uniform and simple procedure primarily without special regard to carcinoma of the lung shows a statistically significant increase in the rate of incidence for males proportional to the increase in mortality rates after the increase of 1940 to 1941 caused by the diagnostic improvements and thus during a period uniform with regard to methods of examination

Since the patients of the Tuberculosis Station are continuously under observation it would seem that they have been the object of maximal medical attention so that the increase in number of cases cannot justifiably be ascribed to increase of medical attention during the years

Summary

If we summarize our conclusions from the studies described it will be seen that since 1920 there has been an increase of cases of carcinoma of the lung in Copenhagen In so far as this increase involves both sexes it may naturally be ascribed to improvements in diagnostic procedures and increased medical attention but this applies only to a small part of the total increase

The main increase is confined to men and ... he ra ... cases verified by histological or postmortem examination were constant In itself this does not exclude that increased medical attention

might have been applied in the same proportion to all degrees of validity of diagnosis, although it would be extremely difficult to explain that increased medical attention should be able to add about twelve per cent every year to the number of cases diagnosed, and that medical attention should be either so much more efficient for men nowadays, or for women in the past, that the recent increase in the number of cases diagnosed should be confined to men

However, it appears that a material of patients suffering from chest trouble and referred for further diagnosis to the Central Tuberculosis Station of Copenhagen directly from practitioners shows an increase in the rate of cases of carcinoma of the lung among men aged over 45 years, which amounts to about hundred times the incidence for all age classes of the general population If we allow for a period of about one year between diagnosis and death, the curve will almost coincide with the curve for mortality among males (*fig 5*) This material has been subject to a maximum of medical attention, and a thorough retrospective revision of the material has in this case ensured that the entire material must be said to have been treated in a uniform way Consequently, it will be impossible to explain the increase in cases diagnosed as lung carcinoma in Copenhagen as caused by anything but a real increase in the number of cases occurring

Studies on the social distribution of cases of carcinoma of the lung in Copenhagen shows a higher incidence than the average among men in quarters of low house rent, and in such quarters the incidence is relatively higher among younger men than elsewhere

Conclusion.

We may then summarize our experience from Greater Copenhagen in stating that there is a steep real increase in incidence of pulmonary carcinoma among males amounting to about 12 per cent yearly, which is independent of progress in diagnostic technique and medical attention

Age Distribution.

INCIDENCE

For the purpose of further studies into the age distribution of cancer of the lung — particularly with a view to the extent to which younger men are affected — we had to turn to the material of death certificates which alone covers a period of a length sufficient for such studies

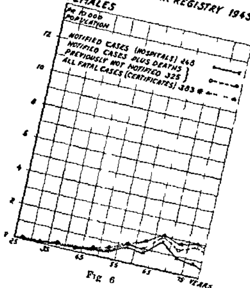


Fig 6

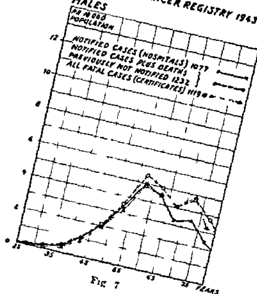


Fig 7

TABLE XVIII

The Danish Cancer Registry 1943-47.
Carcinomas of Bronchus and Lung (162 1 and 163)
Number of cases distributed according to year of first admission or of death (*)

Age	Capital (**)					Provincial Towns					Rural Areas				
	1943	44	45	46	47	1943	44	45	46	47	1943	44	45	46	47
MALES															
24	0	0	0	0	0	1	0	0	0	1	0	0	1	2	0
25-29	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0
30-34	1	0	1	1	0	1	1	1	0	1	0	2	0	1	0
35-39	1	4	1	3	1	3	5	1	4	1	1	2	1	1	0
40-44	8	5	10	11	9	4	2	3	1	2	2	5	7	2	6
45-49	13	16	7	21	17	4	4	5	5	4	4	4	9	10	7
50-54	15	17	25	19	24	6	8	9	13	14	9	8	10	4	12
55-59	18	35	22	38	45	7	6	3	15	11	14	9	7	7	15
60-64	16	16	27	23	39	4	7	9	13	7	9	7	7	8	11
65-69	5	14	8	15	19	2	6	5	8	8	12	4	12	9	9
70-74	8	12	7	14	9	5	6	6	0	5	7	2	11	6	12
75-79	6	4	9	5	8	1	1	1	0	2	0	3	2	5	3
80-84	1	4	1	0	2	0	1	0	3	3	2	0	1	0	1
85	1	1	0	0	0	1	1	0	0	1	0	0	0	0	0
Unknown	4	1	1	0	0	0	0	0	0	0	2	1	0	0	0
Total	96	129	120	150	172	39	48	43	6[illegible]	60	63	47	68	56	76
pr 10000	2.25	3.04	2.81	3.41	3.86	0.83	1.00	0.88	1.24	1.18	0.59	0.44	0.63	0.51	0.69
FEMALES															
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
25-29	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
30-34	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0
35-39	2	1	0	0	1	0	1	0	0	0	1	0	1	2	1
40-44	0	0	0	1	1	0	1	1	1	3	0	0	2	1	1
45-49	1	5	2	0	2	0	1	2	2	0	1	2	0	3	1
50-54	1	1	3	1	1	0	0	0	0	3	3	2	3	3	3
55-59	6	3	3	3	5	3	4	2	2	0	4	4	3	4	6
60-64	3	3	2	3	6	3	1	0	3	1	2	0	5	1	6
65-69	6	1	8	7	7	2	2	3	2	2	7	8	2	4	6
70-74	5	2	1	3	4	0	0	0	2	2	3	4	3	3	1
75-79	1	0	1	2	2	0	1	1	2	1	3	2	2	2	8
80-84	1	0	0	1	1	1	0	0	1	1	1	0	3	0	1
85	1	0	3	0	1	1	0	0	1	1	0	0	0	0	0
Unknown	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0
Total	27	17	23	21	31	10	11	10	16	15	27	24	24	24	36
pr 10000	0.55	0.34	0.46	0.41	0.60	0.20	0.21	0.19	0.29	0.27	0.27	0.24	0.24	0.24	0.35

(*) For cases reported from hospital year of first admission in hospital
For Cases not seen in hospitals year of death
(**) Figures revised.

However, in order to demonstrate the justification of this use of the material of death certificates we bring a corresponding study of the material of cases known to the Danish Cancer Registry (figg 6 9)

It should be noted that for age groups older than 70 years the low number of persons alive will tend to make rates less reliable, and that in the following no conclusions have been based on rates for these age groups

It appears that cases of carcinoma of the lung among women show almost the same increase with age as other cancers with the exception of genital cancers which show a decrease for the older age classes This conclusion is valid both for cases notified from hospitals and for the total of female cases known (3)

TABLE XIX

The Danish Cancer Registry 1943-47
Carcinomas of Bronchus and Lung (162 1 and 163)
(Figures for Capital revised)

Age	Capital	Provincial Towns	Rural Areas	Total
FEMALES		Per 10 000 population		
24	—	—	0 0	0 0
25 29	—	—	0 1	0 0
30 34	—	—	0 1	0 0
35-39	0.2	0 0	0 1	0 1
40-44	0 1	0 3	0 1	0 2
45 49	0 5	0 3	0 2	0 3
50 54	0 4	0 2	0 5	0 4
55 59	1 4	0 9	0 9	1 0
60 64	1 4	0 8	0 7	0 9
65 69	2 9	1 2	1 7	1 9
70 74	2 2	0 6	1 2	1 3
75 79	1 4	1 2	2 2	1 7
80 84	1.3	1 4	1.3	1 3
85	4 9	2 8	—	2 0
Unknown	—	—	—	—
MALES				
24	—	0 0	0 0	0 0
25 29	0 1	—	0 0	0 0
30 34	0 2	0 2	0 1	0 1
35-39	0 5	0 7	0 1	0 4
40 44	2 6	0 7	0 6	1 1
45-49	4 8	1 4	1 1	2 1
50 54	7 5	3 8	1 6	3 6
55 59	14 3	3 7	2 1	5 4
60 64	13 4	4 0	2 0	5 0
65 69	8 3	3 6	2 6	4 1
70 74	10 5	3 9	3 0	4 8
75 79	11.9	1 4	1 7	3 6
80 84	6 8	4 1	1 0	2 8
85	4 7	4 0	—	1 6
Unknown	—	—	—	—

The curve for men, however, shows a peak at the age of 57 Also for this sex there is full coincidence of the curves for cases notified to the Cancer Registry and the material of death certificates even if the decrease of cases admitted in hospitals among the highest age classes is more pronounced *(figg 10 14)*

MORTALITY

As it will appear to anybody comparing the tables given with those in the following there were no important deviations in distribution by age between the material on incidence of cancer of the lung collected by the Cancer Registry and the material of death

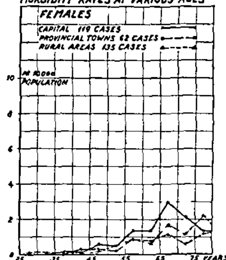


Fig 8

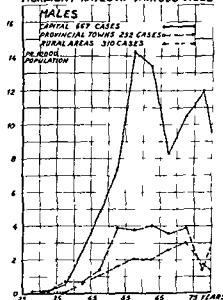


Fig 9

TABLE XX

Cancer of Lung
Mortality per 100,000 living, Denmark

Age	Capital	Prov Towns	Rural Areas	Total	Capital	Prov Towns	Rural Areas	Total
FEMALES		1931 35				1936-40		
0 19	—	0 1	—	0 0	—	0 1	0 1	0 1
20 24	—	—	0 3	0 1	0 4	—	0 6	0 4
25 29	—	0 5	—	0 1	0 8	1 4	0 8	1 0
30 34	0 5	0 6	0 3	0 4	0 4	—	—	0 1
35 39	1 7	—	0 6	0 8	1 0	0 6	1 5	1 1
40 44	3 7	1 4	0 7	1 7	1 1	1 3	0.3	0 8
45 49	6 9	4 0	2 2	3 9	2 5	0 7	2 2	1.9
50 54	6 1	4 5	3 0	4 2	5 0	4 8	3.2	4 0
55 59	10 9	11 5	3 9	7 5	6 3	8 3	7 9	7.5
60 64	12 6	7 5	3 6	6 8	8 7	8 7	8 1	8 4
65 69	15 4	7 6	7 3	9 5	22 8	10 9	7 0	12 2
70 74	16 4	5 9	4 8	8 1	18 6	12 7	14 1	14 [illegible]
75 79	22 7	2 9	5 8	9 4	10 3	5 5	4 2	6.[illegible]
80 84	—	11 2	5 7	5 7	9 8	19 4	5 8	10 6
85	27 4	11 1	6 2	12 3	51 3	—	—	11 2
		1941-45				1946 50		
0 19	—	—	—	—	—	—	—	—
20 24	0 5	—	—	0 1	—	—	—	—
25 29	—	—	—	—	—	—	1 1	0 5
30 34	0 9	—	0 3	0 4	—	0 9	0 3	0 4
35 39	1 9	—	1 7	1 3	1 4	0 5	2 4	1 6
40-44	0 5	2 8	1 5	1 6	1 0	2 0	0 9	1 2
45 49	8 0	3 1	1 0	3 4	4 7	3 9	3 5	3 9
50 54	11 9	8 0	5 7	8 0	9 4	5 6	8 0	7 8
55 59	20 0	11 3	8 1	12 1	15 0	6 6	8 5	9 8
60 64	17 1	16 1	9 2	13 2	17 1	11 6	10 3	12 6
65 69	27 9	17 2	17 4	20 3	23 6	12 2	15 9	17 1
70 74	19 9	22 2	17 0	19 2	21 9	22 9	18 4	20 6
75 79	16 6	9 9	22 1	17 4	21 1	23 2	22 4	22 2
80 84	17 9	18 8	21 2	19 7	45 1	8 4	14 4	21 1
85	30 6	9 8	11 1	15 8	34 7	16 8	4 2	14 9

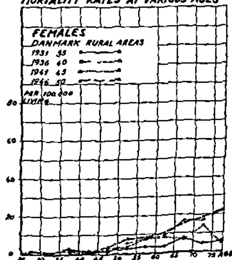


Fig 10

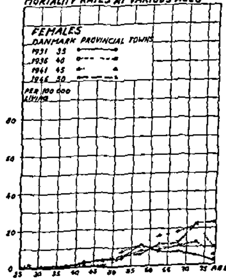


Fig 11

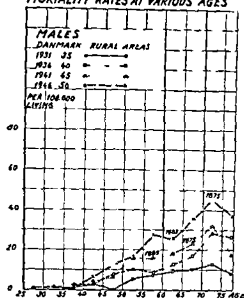


Fig 13

For provincial towns already the period 1936 to 1940 suggests the development of a small peak at the age class 62, representing the cohorts born about 1875 The following period 1941 to 1945 shows a high value at the 57th year for men born about 1885 and

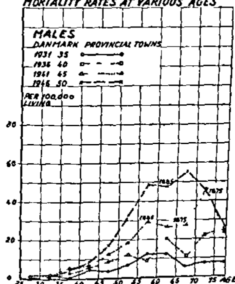


Fig 14

the last period 1946 to 1950 keeps a sharp turn of the curve at the same age, but now representing 1890

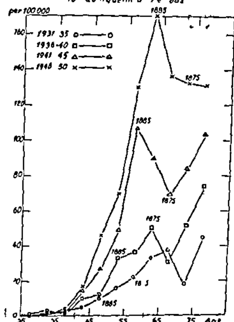


Fig 15

Similar changes appear in the graph for Greater Copenhagen, but in a way which will allow further conclusions The first period

movement now moving to the right and culminating at the age of 62 thus still representing the cohort of 1885

The change in the direction of the move

ped

The significance of the peak must be that the cohort which forms the peak during the

five year period in question is more outstanding in the material than its predecessors and this means that the rise in intensity of the carcinogen must have been steep

Thus we see that the low death rate among the old age classes of the total population is due to the fact that the old people have not been exposed to the carcinogen as effectively as the younger age classes

COHORT STUDIES

In *fig 16* we have plotted the observations [on] deaths from cancer of the lung for Greater Copenhagen in the years 1931 to 1950 which also formed the basis of *fig 15* However the lines of the diagram in *fig 15* have been drawn so as to connect the observations on men born in the same quinquennial period The middle year of these cohorts is indicated

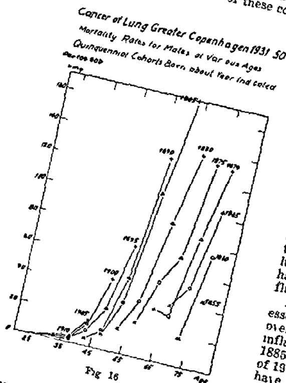


Fig 16

It appears that the curves for the various cohorts are closely similar allowing computation of future mortality for each cohort and subsequently for the total population It will be noticed that the curves for the various cohorts do not coincide as would be the case for most cancers, but move to the left indicating a gradual heavy increase in risk for the younger population This increase seems to have slowed down considerably for the younger cohorts and may now have ceased It would not be explained by assuming that all cohorts were from a certain age subject to some carcinogenic influence unless we add that the influence was strengthened at a certain point of time or during a limited period of years

Now it would seem reasonable to assume that the carcinogenic influences determining the incidence of cancer of the lung, whether they be of customary, occupational or hormonal character, will not begin before the age of 15 or perhaps a few years later From the tables it appears that the cohorts of highest mortality at an early age do not show an increase in rates until after the 35th year of age Consequently it will be justifiable to assume a minimal period of about 20 years from the beginning of the influence to the death of the patient from cancer of the lung under the conditions usual in Copenhagen It follows logically that if we assume a later or earlier beginning of the carcinogenic influence we must respectively shorten or prolong the assumed period with a corresponding number of years It should also be remembered that we must allow for wide variations either way

Under these assumptions and from the observations illustrated in *fig 1* it follows that the increase in mortality from cancer of the lung in Copenhagen beginning in 1931 must have been determined by a carcinogenic influence beginning not later than 1910

It appears from *fig 16* that there is an essential increase in risk from cohort 1875 over 1880 till 1885 so that the carcinogenic influence cannot have begun before cohort 1885 reached the age of 15, i e after the year of 1900 On the other hand the exposure must have started in time for cohort 1860 to be affected at least 20 years before it reached the age of 70 after which the risk increases and this means that the exposure should have begun not later than 1910

It follows from the deliberations given that it is most natural to assume that the carcinogenic factor which causes cancer of the

lung in Copenhagen commenced its action between 1900 and 1910 although it would be a mistake not to allow for rather wide deviations of observations to either side

Vienna and Future Copenhagen

An international comparison will serve to illustrate what is in store for Copenhagen The following diagram represents death rates for cancer of the lung for men in Copenhagen in various periods according to age, and correspondingly for cancer of the respiratory system among men in Vienna as given by Kretz and Ossadnik 1952

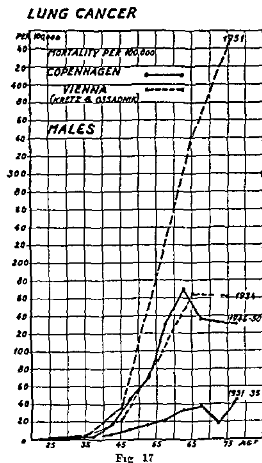


Fig 17

It appears that the age distribution of ... in Vienna for ... Copenhagen ... curves do not show the steep increase for the old age classes usual for extragenital cancers the curve for Vienna 1951 does not deviate so much from the usual type

Sooner or later when the population will consist entirely of cohorts which have been subject to the full carcinogenic influence for the whole of their lifetime, the age distribution of all cases of cancer of the lung will coincide with that of those cohorts and we can now compute the number of deaths from cancer of the lung to be expected under these conditions For this purpose we assume that the cohort born about 1905 represents the final level of carcinogenic influence both with regard to age for the first application and intensity of the latter Second, we assume that the population of Greater Copenhagen will keep its present distribution by age Realities will probably turn out still more unfavourable in both respects The possibility of improvements in therapy is irrelevant in this respect.

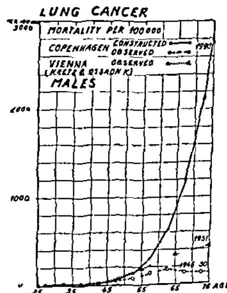


Fig 18

The diagram and *table 22* are computed on these assumptions The shape of the curve has been computed on the basis of the fate of the various cohorts in the Copenhagen population, subject to the carcinogen for various length of time as shown in *fig 18* The level of the curve is adjusted to the level for the cohort born about 1905 It appears that for the first years the curve follows the factual figures for Copenhagen and for some further years the curve for Vienna The level

TABLE XXII

Future Male Mortality from Cancer of the Lung for Greater Copenhagen.
Computed on the basis of the age distribution and mortality of 1946-50 and on the age distribution of lung cancer of various cohorts.

Age	Mean population 1946 50	Smoothed proportions between rates of successive age-classes	Computed annual rates in the future.							
			1951-55	1956-60	1961 65	1966 70	1971 75	1976-80	1981 85	1986-90
25 29	37340	4.9	0 2	0 2	0 2	0 2	0 2	0 2	0 2	0 2
30 34	37340	4 2	1 1	1 1	1 1	1 1	1 1	1 1	1 1	1.1
35 39	39140	3 5	4 7	4 7	4 7	4 7	4 7	4 7	4.7	4 7
40 44	35140	3 0	16 5	16 5	16 5	16 5	16 5	16.5	16 5	16 5
45 49	31140	2 6	49.5	49 5	49 5	49 5	49 5	49.5	49 5	49.5
50 54	28200	2 3	120 1	128 7	128 7	128 7	128 7	128 7	128 7	128 7
55-59	23580	2 1	159 8	276 2	296 0	296 0	296 0	296.0	296 0	296 0
60-64	19140	1 9	273 6	335 6	580 0	621 6	621 6	621 6	621 6	621 6
65 69	15080	1.8	323 6	517.9	637 6	1102 0	1151 0	1181 0	1181.0	1181 0
70 74	10380	1 5	245 9	582 5	932 2	1147 7	1983 6	2125 8	2125 8	2125 8
75 79	6100	1.3	198 6	368 8	873 7	1398 3	1721 5	2975 4	3188 7	3188 7
80 84	2540	1.2	170 4	258.2	479 4	1135 8	1817 8	2237 9	3868 0	4145 3
85-	1060		170 0	204 5	309 8	575 3	1363 0	2181 4	2655 5	4641.6

Computed annual numbers of deaths	
1951 55	241
1956 60	362
1961-65	507
1966 70	660
1971 75	808
1976 80	919
1981 85	979
1986 90	1007

we want to compute will be reached at 1990, and computations show that under the assumptions given, the number of deaths from cancer of the lung in the male population will amount to about 1000, against 168 in 1950, or 852 from all forms of cancer in men in

tail in *table 22*

PROVINCIAL TOWNS AND RURAL AREAS

It appeared from *fig 1* that the rise in deaths from cancer of the lung took its beginning in Danish provincial towns and rural areas respectively about eight and ten years later than in Copenhagen The gradual character of the rise makes it difficult to determine accurately the beginning of the increase, but an analysis of mortality for various cohorts will confirm the impression

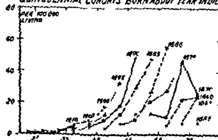


Fig 19

It appears from *fig 19* that the displace-

ment of the curves for provincial towns to younger age classes develop in a way similar to the curves for the capital given in *fig 16* although a little later

Thus, the major displacement of the curves for Copenhagen seemed to have almost ceased with the cohort of 1885 In provincial towns the increase for cohorts earlier than 1875 — although difficult to judge — is not much pronounced while on the other hand there is still some distance between the curves for cohorts born later than the cohort of 1885 so that cohort 1895 takes much the position of 1885 in the diagram for Copenhagen

For rural areas the curves for cohorts given in *fig 21* have not yet taken the more vertical direction and therefore comparisons must be made with some caution It can, however, be distinguished that the gap between the cohorts 1885 and 1890 is well pronounced so that there is no difficulty in assuming that development will continue on the same lines as in the towns although delayed in the start

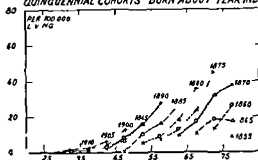


Fig 20

Conclusion

Studies on the age distribution of cancer of the lung show full conformity between the material of the Danish Cancer Registry and mortality figures based on death certificates Cohort studies of the latter material show that if the carcinogenic agent can be supposed not to begin its effect before the age of 15, the period from the beginning of this effect to the death from cancer of the lung of persons exposed will amount to about 20 years or more

Furthermore cohort studies give no reason for assuming any difference in the carcinogenic effect between capital, provincial towns, and rural areas The differences in incidence may be explained by a retardation of about ten years of the carcinogenic effect in provincial towns and rural areas

Causative Agents

HUEPER in his great monograph on Occupational Tumours and Allied Diseases reviews many assumptions offered as explanation of the increase in deaths ascribed to cancer of the lung referring in his turn to SIMONS monograph of 1937 It seems as if this increase began gradually, early in the present century and explanations offered have varied from causation of cancer of the lung by infection with tuberculosis or influenza to carcinogenesis caused by tarring of roads air pollution by combustion engines and the *smoking of tobacco It would seem that* at present we should demand at least some experimental justification of such theories and for these reasons we shall be justified in paying attention primarily to the theory of combustion products as the main cause of cancer of the lung, since there is ample evidence of the carcinogenicity of such products

Within this field it would seem to the authors that the best established evidence of endemiological character has been produced by PERCY STOCKS, 1947 by DOLL and HILL 1950 and 1952, and by WYNDER and GRAHAM, 1950

STOCKS found that the coefficient of correlation between lung cancer death rate and *sunshine hours* for twenty English towns was — 0 690 ± 0 117 The most adequate explanation of his results is that some way or other smokiness of atmosphere is an important factor in producing cancer of the lung

While it is generally reported that air pollution in England was heavier at the beginning of the century than now, it would be perfectly possible to assume a special influence by elements of more recent date such as *combustion products* derived from petrol or perhaps rather from the less refined Diesel oil Atmospheric pollution in the windy climate of Denmark probably never reaches degrees comparable with the English and the complete correspondance between figures for the three larger and the quite small provincial towns taken together with the small dif

ferences from the rural areas on one side and the capital on the other, all of which may be explained as due to differences in the time of appearance of the carcinogenic factor, makes it unnecessary to assume an additional factor like atmospheric pollution as causative of cancer of the lung in Denmark Furthermore it is difficult to see why younger age classes should be more affected than older, as in the Danish material, when a total population is exposed universally to a carcinogenic factor or why women should be exempt from such carcinogenic influence

On the other hand it would seem possible that heavy atmospheric pollution might play a part elsewhere perhaps indirectly through the stimulation of the consumption of tobacco (*cf* MILLS and MILLS PORTER, *1950*), *which* in its turn may increase the number of cases of cancer of the lung

Tobacco

Since it is unlikely that atmospheric pollution plays any important part in the etiology of cancer of the lung in Denmark, the question arises to what extent combustion products from tobacco, which reach the mucosa of the windpipe in higher concentrations than other extraneous agents, are responsible for the proved increase in the frequency of this cancer, which for decades have been held responsible for producing cancer of lip and mouth

The long suspected relation between the smoking of tobacco and cancer of the lung was demonstrated beyond doubt by DOLL and HILL, 1950 and 1952, and WYNDER and GRAHAM, 1950 have independently published corresponding results It may therefore be of interest to examine the applicability of these results on the Danish material which offers good opportunities for a detailed analysis in order to estimate their practical consequences

The Association of the Danish Tobacco Industry in its jubilee publication of 1950 by GLAMANN gives the figures for the annual consumption per head of the various types of tobacco, including imported tobacco, going back as far as 1910 they have been reproduced in *table 23* and graphically represented in *figs 21* and *22*

The diagrams show an enormous increase in the consumption of cigarettes heavy oscillations in the consumption of the usually handmade and relatively lightly taxed cigars, and on the whole constant figures for smoking tobacco Cigarillos, not infrequently smoked by ladies, show gradually increasing figures up to World War II, while the curve for chewing tobacco descends constantly, and the consumption of snuff has been constant but insignificant

TABLE XXIII

Annual consumption in Denmark per inhabitant

Year	Pieces			Kilogrammes		
	Cigars	Cigarillos	Cigarettes	Smoking Tobacco	Chewing Tobacco	Snuff
1910	(91)	(15)	(63)	0 78	0 43	—
1915	(100)	(23)	179	(0 73)	(0 50)	—
1920	102	27	272	0 79	0 45	0 06
1925	76	41	357	0 63	0 33	0 08
1926	73	45	384	0 67	0 32	0 09
1927	67	48	395	0 64	0 30	0 09
1928	64	56	441	0 65	0 28	0 09
1929	79	55	289	0 65	0 28	0 10
1930	82	65	373	0 65	0 27	0 11
1931	80	73	371	0 64	0 26	0 11
1932	75	82	326	0 68	0 23	0 11
1933	87	92	315	0 68	0 21	0 11
1934	100	98	332	0 67	0 20	0 11
1935	110	103	355	0 66	0 20	0 12
1936	117	105	377	0 68	0 19	0 12
1937	122	107	402	0 65	0 18	0 12
1938	124	108	425	0 65	0 17	0 12
1939	128	112	459	0 66	0 16	0 13
1940	107	87	434	0 68	0 15	0 13
1941	59	70	408	0 5?	0 16	0 14
1942	37	81	456	0 67	0 16	0 13
1943	29	72	277	0 43	0 11	0 12
1944	29	76	330	0 46	0 10	0 13
1945	34	83	?88	0 35	0 09	0 14
1946	75	116	524	0 64	0 13	0 15
1947	84	106	574	0 66	0 12	0 13
1948	92	114	635	0 74	0 11	0 13
1949	90	95	825	0 60	0 11	0 12
1950	90	94	938	0 59	0 10	0 11

( ) Uncertain figures

During World War II there was a marked decrease in consumption for all kinds of tobacco, and it is possible that this temporary decrease may influence future figures for cancer of the lung, although individual variations in the time necessary for the development of cancer may tend to veil such oscillations The fact that rations were made

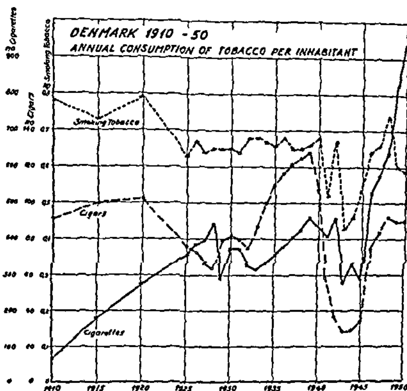

DENMARK 1910 - 50
ANNUAL CONSUMPTION OF TOBACCO PER INHABITANT
Smoking Tobacco
Cigars
Cigarettes

Fig 21

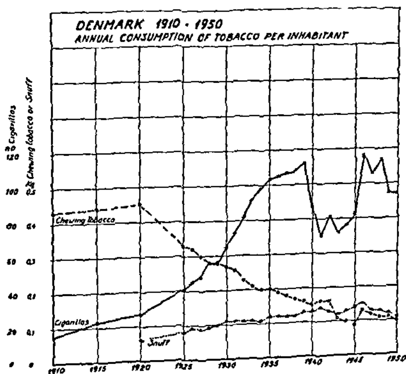

DENMARK 1910 - 1950
ANNUAL CONSUMPTION OF TOBACCO PER INHABITANT
Chewing Tobacco
Cigarillos
Snuff

Fig 22

proportional to previous consumption so that heavy smokers got highest rations may have a similar effect

The steep increase in the consumption of cigarettes between 1945 and 1950 is said by tobacco experts to have occurred, not because of a tendency to increase personal consump tion, but because women have begun smoking cigarettes to a far larger extent than previously It would seem important to have this observation, which we have every reason to trust, documentated with figures with a view to a future rise in the incidence rate for lung cancer among women

A Danish tobacco company has with great courtesy placed at our disposal a market analysis, carried out in January 1948 as an inquiry of 3102 persons by the statistical bu-

TABLE XXIV

Danish Smoking Habits, January 1948, according to « Informa ».

PER CENT OF SMOKERS

	Men	Women
In Capital	90	67
In Provincial Towns	95	71
In Rural Areas	89	54
Total	91	63

TYPE OF SMOKING

Per cent smoking	Men			Women		
	Capital	Prov towns	Rural areas	Capital	Prov towns	Rural areas
Cigarettes	57	50	35	76	78	81
Cigars	22	18	18	2	2	2
Cigarillos	14	10	10	22	20	17
Pipe	23	24	41	—	—	—
Others	—	—	—	—	—	—
Total	116	102	104	100	100	100

	Men			Women			Total	
	30	30-44	45-	30	30-44	45-	Men	Women
Cigarettes	73	51	24	97	87	58	46	79
Cigars	3	16	32	—	2	3	19	2
Cigarillos	3	11	16	3	11	39	11	19
Pipe	28	29	32	—	—	—	30	—
Others							—	—
Total	107	107	104	100	100	100	106	100

DAILY CONSUMPTION OF CIGARETTES

In per cent of all smokers	Men	Women
1	1	5
1 2	15	27
3 4	12	20
5 9	22	25
10 14	29	17
15	21	6
Total	100	100

PER CENT OF SMOKERS

	Men			Women		
	-30	30-44	45-	30	30-44	45-
Cigarettes	93	89	84	76	59	44
Cigars	25	42	24	—	—	—
Cigarillos	67	57	32	—	22	12
Pipe	79	65	30	—	—	—

	Total	
	Men	Women
Cigarettes	89	60
Cigars	30	—
Cigarillos	43	15
Pipe	53	—

reau « Informa » Two similar studies placed at our disposal showed no important deviations from the results of « Informa »'s inquiry, but for technical reasons the latter was most suitable for our investigations

Since this inquiry was undertaken for commercial purposes smokers were defined as in common language, no information was sought on smoking habits in the past, and only cigarette smokers were characterized by figures for their daily consumption In working with the table it should be noticed that when the total of per cent of men with various habits of smoking make figures exceeding one hundred, this is due to some men smoking more than one category of tobacco

It appears from *table 24* that although smokers cover a higher per cent of the male than of the female population this difference is quite out of proportion to the present difference in the frequency of cancer of the lung between the sexes This is not surprising considering that the latter differences will have been determined by the smoking habits of a period at least two decades ago

Similarly, in *table 24* we find practically no difference in the per cent of male smokers between capital, provincial towns, and rural areas, which is in apparent contrast to present differences between these categories in the incidence of cancer of the lung However, since the latter differences, as once demonstrated can be explained as a delay of about ten years in the adoption by the provinces of the carcinogenic habits of the capital, we should not expect any difference in the smoking habits of 1948

But even in spite of the long period we must assume between the adoption of smoking and the death of smokers sensitive to the carcinogenic effect we still find an increased per cent of cigarette smokers among younger men and in the capital, or just in those parts of the population in which cancer of the lung is most frequent at present Also younger women prefer cigarettes to cigarillos which are more favoured by the older The former finding might be explained by assuming that younger men have gradually increased their consumption of cigarettes, anyhow as a group and that this process is still going on Another explanation would be that men are inclined to change their habits of smoking as they get older, but the continuous increase in the general consumption of cigarettes would seem to speak against this hypothesis, although it must be remembered that the consumption figures refer to the whole country, so that this cannot be taken as a proof

The corresponding question for cigars is more difficult to deal with on account of the oscillations in consumption, but appears easier to answer for pipe smokers This way of smoking, so common in rural areas, is nearly equally frequent among all age classes, and since the consumption has been correspondingly constant since 1910, it seems as if pipe smokers are disinclined to change their habits of smoking However, these deliberations should not be pressed too far On closer examination one would probably find a change in favour of shag pipes during the last decades

Finally, it appears from *table 24* that younger men and women are more inclined to inhalation of tobacco smoke than the older generation, which would be expected because inhalation on the whole will follow the use of cigarettes

Occupation.

In consequence of DOLL and HILL's and WYNDER and GRAHAM's studies it would seem that any demonstration of an increase in frequency of cancer of the lung on an occupational basis except for chromium workers etc must be preceeded by an examination of the smoking habits of the occupation in question, in order to exclude that special occupational opportunities for excessive consumption of tobacco might play a part

With this — somewhat theoretical — reservation we have in *tables 25* and *26* given some figures respectively for various occupations in Denmark 1943 to 1947 and for master artisans which seem particularly exposed The latter table gives a specification for Copenhagen 1943 to 1947

Conclusion.

From the statistical material available it seems impossible to explain how atmospheric pollution could cause the differences found in frequency of cancer of the lung between various parts of the Danish population, especially between towns and country, men and

TABLE XXV

The Danish Cancer Registry 1943-47
Cancer of Bronchus and Lung (162.1 and 163) — Capital
Occupations of a proportion numerically exceeding two, between deviation from the computed and standard deviation

	Capital obs./comp.		Prov. towns obs./comp.		Rural areas obs./comp.		Whole country obs./comp.	
MALES								
Small holders	0	0.1	2	3.2	31	46.4	33	49.7
Fishermen	0	1.4	3	4.3	1	5.0	4	10.6
Farmers (no specification)	0	0.7	1	2.2	4	8.3	5	11.2
Master artisans (*)	46	30.9	28	17.7	28	16.7	102	65.3
Workers in paper and graphic industries	17	15.1	5	3.1	5	1.0	27	19.1
Workers in unstated industries	45	58.3	25	36.1	29	41.3	99	135.6
Architects	2	1.3	3	0.6	0	0.2	5	2.1
Journalists	5	3.0	3	0.6	0	0.0	8	3.6
No occupation (old age and invalidity pension)	5	8.5	2	8.7	9	15.6	16	32.7
FEMALES								
Workers in paper and graphic industries	5	2.1	2	0.6	1	0.4	8	3.1
Nurses, childrens nurses, masseuses etc.	2	0.7	1	0.3	1	0.3	4	1.4
Assistants	5	1.2	1	0.3	0	0.4	6	1.9

(*) The group «Master artisans» divided into special professions is given in the continuation of this table

TABLE XXVI

Master artisans

	Number	Obs.	Comp.
Bakers and confectioners	836	5	2.0
Butchers	528	1	1.3
Tailors	874	6	2.1
Shoemakers	953	1	2.3
Bricklayers (master builders)	631	4	1.5
Carpenters	436	1	1.1
Painters and decoraters	1077	5	2.6
Joiners	1165	7	2.9
Glaziers	302	4	0.7
Gold and silversmiths	273	0	0.7
Watch and Instrument makers	238	0	0.7
Plumbers	382	2	0.9
Smiths and Metal workers	1173	5	2.9
Bookbinders	276	1	0.6
Photographers	183	0	0.5
Hairdressers and barbers	895	2	2.2
Other master artisans	2406	2	5.9
Total	12628	46	30.9

women, and between the different age classes in Copenhagen.

On the other hand, an analysis of smoking habits on the basis of an inquiry undertaken for commercial purposes seems in full conformity with the possibility that the adoption of cigarette smoking in the beginning of the century may directly or indirectly have caused the increase in incidence of cancer of the lung.

There appears some difficulty in connecting such an effect of tobacco with the smoking of pipes.

The absence of a surplus of male cases of cancer of the lung in Denmark before 1931 suggests that the smoking habits must have been without carcinogenic effect up to a time preceeding that year with the average time necessary for the development of cancer of the lung, i.e. twenty years or more.

Summary.

Studies based on materials of death certi-

ficates from the Danish National Health Ser vice the Danish Cancer Registry and the Central Tuberculosis Station of the City of Copenhagen have shown beyond doubt a steep real increase in incidence of bron chogenic cancer among males particularly in Greater Copenhagen which at the moment

the younger age classes among the poorer part of the population

There is full conformity in distribution by age between the material from the Tubercu losis Station from the Danish Cancer Re gistry and mortality figures based on death certificates Cohort studies of the latter show that if the carcinogenic effect can be assu med to take its start not earlier than at the age of fifteen years the period from the be

TABLE I.

Distribut on by Age of Population in Denmark — given as average for qu nquennial per ods

FEMALES

Age	1931 35			1936 40		
	Capital	Prov towns	Rural areas	Capital	Prov towns	Rural areas
0 19	11? 640	143 040	379 060	115 070	146 640	361 110
20 24	43 760	42 460	78 780	45 890	43 540	69 830
25 29	44,080	39 720	73 000	48 180	4? 110	74,150
30 34	40 5?0	35 780	69,300	44 600	39,380	71,5?0
35 39	36 ?80	31 800	64 860	40 ?00	35 970	67 470
40 44	32 060	28 080	57 0?0	35,930	31,930	62 700
45 49	28 940	25 180	53 460	31 460	27 700	54,960
50 54	?6 080	?? 360	46 680	27 9?0	?5 0?0	50 790
55 59	21 940	19 1?0	41 360	?5 250	21 740	43,230
60 64	17,520	16 080	33 720	?0 700	18 4?0	36 880
65 69	14,320	13 ?00	27,280	15 780	14 750	28,590
70 74	10 980	10 ?40	20 980	11 830	11 0?0	31,310
75 79	7 060	6 960	13 7?0	7 740	7 ?80	14 140
80 84	3 330	3 560	7 000	4 090	4 1?0	6 950
85	1 460	1,800	3 240	1 560	1 630	3 970
Total	441 0?0	439 380	969 460	476 ?30	471,250	967 600
	1941 45			1946 50		
0 19	115 000	151 200	360 400	129 380	175 880	370 080
20 24	43 460	47 720	7?,8?0	39 400	45 580	68 300
25 ?9	45 400	43 ??0	69 780	43 960	46 400	7? 160
30 34	45 740	4? 440	74 480	43 740	42 700	71 ??0
35 39	42,380	39 200	71 160	44 200	41 880	74 040
40 44	39 140	36 180	65 8?0	41,8?0	39 040	69 660
45-49	35 000	3? 300	60,340	38 4?0	36 1?0	63 6?0
50-54	30 300	27 600	5? 5?0	34 140	31,900	57,640
55 59	27 060	24 780	47 040	29 ?80	?7 3?0	49 440
60 64	23 380	21 140	39 120	25 680	?4 100	4? 540
65-69	18 660	17 400	31 040	21 160	19 740	33 9 0
70-74	13 040	1? 620	2?,3?0	15 540	14 8?0	?5 000
75 79	8 440	8 120	14 480	9 500	9 480	16 100
80 84	4 460	4 ?60	7 560	4 880	4 780	8,3?0
85	1 960	? 050	3 60?	2,304	2 388	4 7??
Total	493 420	510 ?30	992 48?	5?3 014	56? 1?8	10?6 ?

ginning of this effect to the death from cancer of the lung of persons exposed will amount to about twenty years or more under the conditions examined In the capital the effect must have begun about 1900 to 1910

On the basis of the cohort studies the differences in incidence of cancer of the lung found between towns and country can be explained by a retardation of about ten years in the beginning of the carcinogenic effect in provincial towns and rural areas

From the material available it seems impossible to explain how atmospheric pollution could cause the differences found in frequency of cancer of the lung between various parts of the Danish population especially

On the other hand an analysis of smoking

TABLE II

Distribution by Age of Population in Denmark — given as average for quinquennial periods

MALES

Age	1931 35			1936 40		
	Capital	Prov towns	Rural areas	Capital	Prov towns	Rural areas
0 19	108 720	137 340	401 180	111 050	140,990	386 0[illegible]0
20 24	35 660	34 [illegible]20	92,520	38 110	35 600	85 650
25 29	35 800	33 820	80 400	41 100	37 170	83 730
30 34	32 560	31,240	72 760	37 370	35 660	76 870
35 39	30 240	28 520	65 080	33 410	32 260	70,290
40 44	26 880	25,380	56 940	30 050	28 990	63,380
45-49	23 480	2[illegible] 980	53 900	26 230	25 390	55,340
50 54	20 800	20 520	48 490	22 630	22 700	51,590
55 59	17 480	17 240	43 960	19 430	19 760	45 730
60 64	13 280	13 900	35 200	15 800	16 320	39 780
65 69	9 660	10 820	27 480	11 220	12 520	30 280
70 74	6 720	8 060	21 140	7,380	8 900	21,5[illegible]0
75 79	4 020	5 360	14 020	4 320	5 6[illegible]0	14 390
80 84	1 780	2 660	6 960	2 050	3 010	7,360
85	620	1 180	2 940	660	1 200	3 640
Total	367 700	393 540	1 022 960	400 890	426 140	1 035,5[illegible]0
	1941 45			1946 50		
0 19	113 960	148 2[illegible]0	382 960	120 880	174 300	396 880
20 24	36 200	39 600	89 440	34 060	36 880	82 200
25 29	38 700	38 760	80 140	37,340	41 490	80 420
30 34	39 640	40 260	80 990	37,340	40 220	77 780
35 39	36 200	36 840	75 560	38 140	40 380	80 080
40 44	3[illegible] 060	32 660	69 290	35 140	36 580	74 360
45-49	29 440	29 280	60 990	31 140	32 400	67 460
50 54	25 080	25 020	53 220	28 200	28 700	59 760
55-59	21 160	22 080	48 5[illegible]0	23 580	24 200	[illegible]0 600
60 64	17,580	18 520	41 600	19 140	21 020	44 720
65 69	13 840	15 200	33 860	15 080	17 380	36 580
70 74	8 780	10 620	3 600	10 880	12 [illegible]80	27 460
75-79	4 940	6 600	14 760	6 100	7 680	17,090
80 84	2 220	3,200	7 560	2 540	3 720	7 740
85	824	1 482	3 570	1 060	1,552	4 820
Total	420 624	468 642	1 066 030	449 620	519,272	1 106,940

TABLE III

Cancer of Lung (162 162 0 and 163) Denmark 1931 51
Crude mortality per 100 000 population Denmark

MALES

Year	Capital abs	Prov towns abs	Rural areas abs	Capital per 100000	Prov towns per 100000	Rural areas per 100000	Total per 100000
1931	16	8	16	4 5	2 1	1 6	2 3
32	19	6	21	5 3	1 6	2 1	2 6
33	27	15	15	7 4	3 8	1 5	3,2
34	20	11	19	5 3	2 7	1 9	2 8
35	35	13	23	9 2	3,2	2 °	3 9
1936	23	13	30	5 9	3 1	2 9	3 6
37	46	16	36	11 6	3 8	3 5	5 3
38	36	10	36	8,9	2,3	3 5	4 4
39	55	25	40	13 5	5 8	3 9	6 4
40	53	25	50	13,0	5 7	4,8	6,8
1941	63	34	33	15 3	7 6	3 1	6 8
42	98	43	47	23 5	9 4	4 5	9 7
43	85	36	57	20 1	7,7	5 4	9 1
44	108	38	55	25 4	7 9	5 1	10 1
45	96	39	74	22 5	8 0	6 8	10 5
1946	1°8	63	65	29 1	12 6	6 0	12 6
47	141	63	71	31 6	12 4	6 4	13 4
48	148	53	86	3° 8	10 °	7 8	13 8
49	176	57	93	38 7	10 7	8 4	15,5
50	168	73	113	36 9	13 5	10 1	16 7
1951							18 4

TABLE IV

Cancer of Lung (162 162 0 and 163) Denmark 1931 51
Crude mortality per 100 000 population Denmark

FEMALES

Year	Capital abs.	Prov towns abs	Rural areas abs.	Capital per 100000	Prov towns per 100000	Rural areas per 100000	Total per 100000
1931	16	7	9	3 7	1 7	0 9	1 8
32	18	9	13	4 1	2 1	1,3	2 2
33	13	7	6	3 0	1 6	0 6	1 4
34	21	10	13	4 7	2 °	1 3	° 4
35	13	11	14	2 8	2 4	1 4	2 0
1936	16	7	17	3 4	1 5	1 8	2 1
37	19	8	24	4 0	1 7	2 5	2 7
38	17	11	18	3 6	2 3	1,9	2 4
39	10	14	16	2 1	2 9	1 7	° 1
40	13	12	13	2 7	2 5	1 3	2 0
1941	26	14	20	5 4	2 8	2 0	3 1
42	31	19	29	6 3	3 8	3,0	4 0
43	26	24	29	5 2	4 7	°,9	4 0
44	23	14	29	4 6	2 7	2 9	3,3
45	34	19	32	6 8	3 6	3 2	4 2
1946	16	23	2°	3 1	4 2	2 2	2 9
47	37	18	37	7 1	3,3	3 6	4 4
48	30	10	33	5 7	1 8	3 °	3,5
49	30	19	36	5 7	3,3	3 5	4 0
50	28	20	41	5 3	3 4	3 9	4 1
1951							4 3

habits on the basis of an inquiry undertaken for commercial purposes is in full conformity with the possibility that the adoption of the smoking of cigarettes in the beginning of the century may directly or indirectly have caused the increase in incidence of cancer of the lung, while there is some difficulty in connecting such an effect of tobacco with the smoking of pipes, as such

The absence of a surplus of male cases of cancer of the lung in Denmark before 1931 suggests that smoking habits here must have been without carcinogenicity up to a time preceeding that year with the average time necessary for the development of cancer of the lung, i e about twenty years or more

DISCUSSION

DR LEVIN I think Dr Clemmesen should be congratulated on the type of studies he has made and the way he has conducted his research He has shown unusual industry and imagination

DR DE MUYLDER Dr Clemmesen attributes importance to some of the oscillations in the series of curves he showed but not to others Is the importance attributed to such and such an oscillation due to a worked calculation or more impressions ?

DR CLEMMESEN It is all based on calculation

DR KRETZ Have you found any relationship between squamous celled carcinoma and adenocarcinoma and the use of tobacco ?

DR CLEMMESEN I believe that the increase in cancer of the lung is mainly due to cancers of squamous cell origin, although the statement is abo t an ncrease of « non ade- [illegible]

[illegible] The proof to this effect must be sought in Dr Doll s studies

DR DENOIX In the graphs comparing mortality figures for Holland and Denmark since 1920 were the variations in the composition of the population taken into account ?

DR CLEMMESEN The figures were taken from Dr Korteweg's paper They can only be regarded as crude mortality figures although age distribution of men and women will usually follow each other

DR DENOIX As a result of an inquiry into morbidity figures in France, we found the distribution of histological forms was 59 per cent squamous-celled carcinoma, 23 per cent adeno carcinoma, 8 per cent oat-celled carcinoma, and 10 per cent of various other forms

DR DE MUYLDER What are your criteria for distinction between adeno-carcinoma, anaplastic carcinoma, and the other kinds of cancer ?

DR CLEMMESEN The terms have just been given as they were stated by various pathologists in Copenhagen There were a number of cases termed « solid » which may belong both to the squamous type and to the anaplastic forms For this reason we prefer to make statements just on « adenomatous » and « non adenomatous » forms We hope to make a more detailed study on a material of many cases grouped by a single man

DR SMITH It seemed to me from Dr Clemmesen's figures that the squamous or non adenomatous tumours comprise by far the majority of tumours in the middle age groups, whereas in the young and very old there seemed little difference in the proportion of the different types of tumours Is that what was intended ?

DR CLEMMESEN It seems that wherever there is an increase of cancer of the lung it is the non adenomatous part which increases, and the adeno carcinomas remain almost the same, although with some increase in older age groups, but I would not like to go too far in my conclusions

DR MAISIN We have all been working with carcinogens and we know perfectly well that the same carcinogen in a pure strain of animals can induce tumours of quite different histological type You can have oat-celled or anaplastic carcinoma or epidermoid carcinoma arising in the same strain of mice induced by the same carcinogen Another point In the same large tumour you can find areas of different degree of differentiation and of different histological types Any kind of epithelial cells may leave various types of tumour If a tumour is really anaplastic no one can tell where it comes from I think if we want to achieve anything on these graphs we will have to use the same

grading methods Grade I, II, III, IV — the well-known gradings of Broders — may be applied as well to adeno-carcinoma as to other types of tumours But even with the best grading method or the most scientific type of nomenclature it will be difficult actually to establish any kind of relationship in one type of carcinoma with a definite carcinogen agent

DR CLEMMESEN I agree with Professor Maisin

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ZUSAMMENFASSUNG

Die genaue Analyse der Todesbescheinigungen des « Danish National Health Service », der zentralen Tuberkulosestation der Stadt Kopenhagen und der « Danish Cancer Registry » zeigte eine sichere Zunahme des Lungenkarzinoms, insbesondere in Gross Kopenhagen wo es gegenwartig einen Prozentsatz von 12 % erreicht hat Die Zunahme wird festgestellt unabhangig von der verbesserten Diagnostik sie findet sich ganz besonders in jungeren Altersklassen der armeren Bevolkerungsschicht und vor allem fur die nicht adenomatosen Geschwulsttypen Zwischen den Angaben der « Danish Cancer Registry » und denjenigen der Todesbescheinigungen besteht vollige Uebereinstimmung Daraus geht hervor dass die Latenzzeit zwischen dem Einsetzen des karzinogenen Effekts der nicht vor dem Alter von 15 Jahren angenommen wird [illegible] ungefahr 20 Jahre [illegible] ef [illegible] nz des Auftretens des Lungenkrebses zwischen Stadt und Land dadurch erklart werden dass der Beginn des karzinogenen Effekts in Provinzstadten und landlichen Gegenden etwa zehn Jahre spater liegt

Es scheint unmoglich zu sein dass bei dem vorliegenden Material atmospharische Einflusse die Ursache sein konnten fur die festgestellten Differenzen beim Lungenkarzinom zwischen den verschiedenen danischen Bevolkerungsschichten insbesondere zwischen Stadt und Land Mann und Frau und zwischen den verschiedenen Altersklassen bei den Mannern in Kopenhagen

Andererseits lasst sich mit einer Analyse der Rauchgewohnheiten an Hand der Handelsstatistiken [illegible] ware

Das Fehlen eines Ueberwiegens des Lungenkarzinoms bei Mannern in Danemark vor 1931 lasst vermuten, dass die Rauchergewohnheiten ohne karzinogenen Effekt waren vor diesem Jahr, abzuglich die fur die Entwicklung des Lungenkarzinoms notwendige durchschnittliche Zeit von 20 Jahren und mehr

SUMMARY

Studies based on materials of death certificates from the Danish National Health Service the Central Tuberculosis Station of the City of Copenhagen and the Danish Cancer Registry have shown beyond doubt a steep real increase in incidence of bronchogenic cancer among males particularly in Greater Copenhagen which at the moment amounts to about twelve per cent yearly The increase is found irrespective of changes in diagnostic means and is most pronounced for the younger age classes among the poorer part of the population and most pronounced for cancer of non adenomatous types

There is full conformity in distribution by age

earlier than at the age of fifteen years the period from the beginning of this effect to the death from cancer of the lung of persons exposed will amount to about twenty years or more under the conditions examined In the capital the effect must have begun about 1900 to 1910

On the basis of the cohort studies the differences in incidence of cancer of the lung found between towns and country can be explained by a retardation of about ten years in the beginning of the carcinogenic effect in provincial towns and rural areas

From the material available it seems impossible to explain how atmospheric pollution could cause the differences found in frequency of cancer of the lung between various parts of the Danish population especially between towns and country, men and women and between different age classes among men in Copenhagen

On the other hand, an analysis of smoking habits on the basis of an inquiry undertaken for commercial purposes is in conformity with the possibility that the adoption of the smoking of cigarettes in the beginning of the century may directly or indirectly have caused the increase of cancer of the lung, while there is some difficulty in connecting such an effect of tobacco with the smoking of pipes.

The absence of a surplus of male cases of cancer of the lung in Denmark before 1931 suggests that smoking habits here must have been without carcinogenicity up to a time preceeding that year with the average time necessary for the development of cancer of the lung i e about twenty years or more

RESUMEN

Estudios basados en el análisis de los certificados de defunción emitidos por Servicio Nacional Danés le Sanidad la Estación Central de Tuberculosis, el Ayuntamiento de Copenhague y el Registro Danés del Cancer han demostrado un aumento brusco real de la frecuencia del cancer de pulmon sobre todo en el Gran Copenhague que en la actualidad alcanza aproximadamente el 12 % anual Este aumento no depende de las variaciones de los medios diagnosticos y es mas pronunciado en las clases de edad mas joven en la parte mas pobre de la poblacion y mas pronunciada para el cancer de tipo no adenomatoso

Existe completa conformidad en la distribucion por edades entre el material del Registro Danes del Cancer y las cifras de mortalidad basadas en certificados de defunción Los estudios de cohortación de este ultimo muestran que si el efecto carcinogeno puede suponerse que empieza a actuar no antes de los quince anos de edad el periodo desde el comienzo de este efecto hasta el fallecimiento por cancer de pulmon de las personas expuestas alcanzará la cifra de 20 anos o mas en las condiciones del examen En la capital el efecto ha debido iniciarse hacia 1900 o 1910

Segun los estudios de cohortacion las diferencias en la frecuencia del cancer de pulmon entre las ciudades y el campo pueden explicarse por un retraso de unos diez anos en el comienzo del efecto carcinogeno y las ciudades provincianas y las zonas rurales

Segun el material disponible parece imposible explicar como las poluciones atmosfericas pueden determinar las diferencias en frecuencia del cáncer pulmonar entre varias partes de la población danesa, especialmente entre ciudades y campo, mujeres y hombres y entre las diferentes clases de edad entre los hombres en Copenhague

Por otra parte el analisis de las costumbres en el uso del tabaco segun una encuesta realizada con fines comerciales esta de acuerdo con la posibilidad de que el uso de cigarrillos al comienzo de siglo haya determinado directa o indirectamente el aumento del cancer pulmonar si bien no es facil relacionar dicho efecto del tabaco con el hecho de fumar en pipa.

La falta de un predominio de casos masculinos de cancer pulmonar en Dinamarca antes de 1931 parece indicar que el fumar no ha tenido acción carcinogena hasta una fecha anterior a dicho ano con el tiempo medio necesari para el desarrollo del cáncer pulmonar o sea veinte o mas anos

RESUME

Des etudes basees sur l analyse des certificats de deces emis par le Danish National Health Service, the Central Tuberculosis Station of the City of Copenhagen et le Danish Cancer Registry, ont montre une augmentation certaine aigue de l incidence du cancer du poumon et ce plus specialement et plus particulièrement dans le grand Copenhague ou l on observe

actuellement un taux de 12 % L'accroissement du taux des malades n'est pas fonction des modifications des méthodes de diagnostic, il est plus marqué pour les éléments les plus jeunes des classes pauvres de la ville et est plus prononcé pour les cancers du type non adénomateux

Il y a une concordance parfaite entre la distribution du cancer du poumon exprimé, d'une part, sur la base du Danish Cancer Registry et d'autre part, sur la base des certificats de décès L'étude coordonnée de ces derniers chiffres montre que les effets cancérigènes ne se manifestent pas avant l'âge de 15 ans, la période qui s'écoule entre le debut de ces manifestations et la mort par cancer du poumon chez les personnes exposées, est d'environ 20 ans ou plus ceci, dans les conditions étudiées Dans la capitale, l'effet doit avoir commencé entre 1900 et 1910

En se basant sur l'étude des cas par groupes, les differences d'incidence du cancer du poumon entre les villes et les régions rurales peuvent s'expliquer par un retard d'environ 10 ans quant au debut de l'action cancérigène entre les villes de province et les régions rurales

Il paraît impossible, en se basant sur le matériel dont on dispose, d'expliquer comment un air pollué peut être cause des differences établie dans la fréquence du cancer du poumon dans les diverses populations du Danemark specialement entre celles des villes et des campagnes, entre hommes et femmes et par catégorie d'âge chez les hommes de Copenhague D'autre part, en se basant sur l'analyse des différentes façons de fumer, en concordance avec une enquête entreprise dans des buts commerciaux, il apparaît que le fait d'avoir, au début de ce siècle, adopté la cigarette, pourrait bien être, directement ou indirectement lié à l'accroissement des cancers du poumon, ... ne relation iden ... imer la pipe ... les hommes, de cas de cancers du poumon avant 1931 fait penser que *les différentes façons de fumer dans ce pays* doivent avoir été sans action sur la carcinogenèse jusqu'à la période de temps précédant cette année et pendant une periode moyenne nécessaire au développement du cancer du poumon, c'est à dire pendant une période d'environ 20 ans

RIASSUNTO

L'esame dei certificati di morte rilasciati dall'Uf ...

Registro ...

l'aumento rapido della frequenza del cancro del polmone nel sesso maschile, in modo particolare in Co- ...

per i soggetti piu giovani tra la popolazione povera ed e più pronunciata per le forme maligne di tipo non adenomatoso

Vi è una completa concordanza nella distribuzione del cancro del polmone tra il materiale del Registro danese del cancro e quella che risulta dai certificati di morte Lo studio coordinato di queste ultime cifre dimostra che gli effetti cancerogeni non si manifestano prima dei 15 anni, il periodo che intercorre tra l'inizio di queste manifestazioni e la morte per cancro del polmone nelle persone esposte è valutato a circa 20 anni o piu nelle condizioni prese in esame Nella capitale l'effotto deve aver acuto inizio tra il 1900 e il 1910

Basandosi sullo studio dei casi divisi in gruppi le differenze di frequenza del cancro del polmone tra le città e le zone rurali possono esplicarsi con un ritardo di circa 10 anni, quanto all'inizio dell'azione cancerogena tra le città di provincia e le regioni rurali Sembra impossibile, basandosi sul materiale reso disponibile, di spiegare come nel pulviscolo atmosferico vi possano essere cause differenti in rapporto alla frequenza del cancro del polmone tra le varie parti della popolazione danese, in particolare tra quelle delle città e delle campagne, fra le donne e gli uomini e, in rapporto alle differenti età, tra gli uomini in Copenhagen D'altra parte riferendosi all'analisi delle abitudini del fumo, in base all'inchiesta intrapresa sul materiale messo in commercio, risulta che l'abitudine di fumare le sigarette all'inizio del secolo possa direttamente o indirettamente aver causato l'aumento del cancro del polmone, mentre vi è difficoltà a mettere in rapporto tale aumento con l'abitudine di fumare la pipa

L'assenza di una prevalenza nell'uomo del cancro del polmone prima del 1931 permette di considerare che le differenti abitudini del fumo in questo paese debbano non aver influito sulla carcinogenesi fino al periodo precedente a tale data e durante un periodo medio necessario allo sviluppo del cancro del polmone, vale a dire in un periodo di circa 20 anni

Il nous a été impossible, par suite de circonstances indépendantes de notre volonté, de faire figurer la totalité des traductions des Résumés

Nous le regrettons et nous en excusons vivement

La Rédaction